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ROLF SIEVERT

ON HIS FIFTIETH BIRTHDAY

May 6th, 1946

The history of medical radiation physics in Sweden is the story of ROLF SIEVERT and his school.

The beginning of the nineteen-twenties was, in Sweden as throughout the world, a critical period for radiotherapy. Deep roentgen and radium therapy had become definitely established when radiological research blossomed out once more after the first World War, and radiologists were faced with new and intricate problems of treatment and new dangers which they felt that they could not master single-handed.

Our measuring instruments were of foreign manufacture and were, it is true, excellent in many respects for their time, but they were unsuited to the new tasks awaiting them. Swedish radiologists were entirely dependent on their own incomplete knowledge of radiation physics and electrotechnics in their attempts to further independently the development of radiotherapy.

It became more and more evident that radiotherapy needed the steadfast support of radiophysics, and laboratories for radiation physics under the leadership of qualified physicists had grown up in the most advanced radiotherapeutic centres of the cultural world. The time of teamwork in radiotherapy was at hand. At »Radiumhemmet», however, we had neither the means nor the space for radiation research, nor had we any radiation physicists at our disposal. But at this juncture ROLF SIEVERT appeared on our horizon, and he came to us with his arms loaded with just such gifts.

I met ROLF SIEVERT for the first time during a study trip to the United States in the summer of 1920. He was there in order to survey the latest advances in the field of physics in America, and I flitted like a bee from flower to flower in the radiological garden of the New World. He was deep-

ly impressed by the possibilities for development in radiation physics, and I in my turn by the importance of team-work for medical radiology. And so it came about that our paths crossed in Schenectady, the stronghold of radiological technics in America. There, in a hotel room high up among the stars, we sat throughout an entire night and compared our observations and our plans, and there were laid the foundations of a friendship and a companionship in the service of radiology which has lasted ever since.

At »Radiumhemmet» we could only dispose of one small room for physical control work, but SIEVERT placed himself and his own private physical laboratory at the disposal of Radiumhemmet for radiophysical research work. For four years, Radiumhemmet had — as it is recorded in the annual report of the Cancer Society — »the benefit of voluntary and unpaid collaboration» with this radiation physicist, »who assisted the Home in controlling the roentgen dosage and constructed for this purpose extremely valuable instruments, and also carried out research at Radiumhemmet on the dosage problem». In 1923, The Cancer Society of Stockholm decided to enlarge Radiumhemmet with a building which would contain — as well as a laboratory for pathological anatomy, a library and a museum — a small department for medical radiation physics. This was opened on July 5th., 1924. SIEVERT conjured forth »anonymous donors» who provided 30,000 Crowns »as a contribution to the upkeep and expenses of the physical institute for the next five years, with the proviso that the Cancer Society should procure funds for complete equipment of the institute, and also guarantee its maintenance and upkeep for a period of five years».

As from July 1st., 1924, SIEVERT was appointed »Head of Radiumhemmet's physical laboratory» and devoted, each year, as long as he was in the service of the Cancer Society, his salary and far more in addition, to the support of the research work of the laboratory. Dr. ROBERT THORÆUS, the roentgen physicist, was appointed from January 1st., 1927, as SIEVERT's first assistant.

In 1929, Radiumhemmet was expanded with a new ward, and an entire floor was then fitted out with spacious and well-equipped rooms for the radiophysical institute. At the same time SIEVERT enlarged his own laboratory, and moved to the immediate vicinity of Radiumhemmet. He had by then a well-established reputation in his own scientific field, and there was no lack of funds for research at his institute. Students thronged to him, and as early as 1931, he had five »extra assistants» working in the physical laboratory. Amongst them were the radium physicist, SVEN BENNER, and the chemist and radiation biologist, ARNE FORSSBERG, who — together with ROBERT THORÆUS — have been SIEVERT's coworkers since that time.

When, in 1937, Radiumhemmet was transferred to Stockholm's new University Hospital, »Karolinska Sjukhuset», the radiophysical and the radiopathological laboratories were merged with the teaching hospital as independent state institutes. SIEVERT has now at the Radiophysical Institute a staff of six permanently-employed scientists, as well as laboratory assistants and clerical staff, etc. The Cancer Society and King Gustaf V's Jubilee Fund have borne the entire cost of the erection and equipment of these scientific institutes. They have been handed over to the State, which pays for their maintenance, with the assistance of the above-named Foundations.

Such are the rough outlines of the course of ROLF SIEVERT's career in the service of medical radiation physics. I shall now attempt to draw a rapid sketch of the work he has carried out within the framework of these events.

SIEVERT has, in his work as a constructor, research-worker and organizer, laid new grounds in the field of medical radiation physics.

His wealth of ideas and constructive skill have given birth to new measuring instruments and apparatus for radium treatment, which have opened up new vistas in measuring technique, not only in radiological research work, but also in dosage, and protection measures in practical radiotherapy.

His »radium compensator» overcame the difficulties in the measurement of radiation intensity with small ionisation chambers in the immediate vicinity of radium preparations, and his portable »roentgen compensator» is the kernel of the collection of instruments he has designed for the circulating control of radiological work.

SIEVERT's constructions for the further development of LYSHOLM's »radium gun» for teleradium treatment are of great practical significance, especially his genial solution of the difficult problem of effective protection against radiation for workers giving treatment with this apparatus. He has also introduced a new material — iron-ore concrete — for use in the walls and roofs of the teleradium laboratories for protection against radiation.

SIEVERT's insulated »condenser chamber» which he has designed in a large number of models for very varying fields of radiological measuring technique, has been of the greatest importance not only for SIEVERT's own research, but also for the development of the technique of measuring and dosage in radiation treatment.

It is generally known that it is difficult, and in many cases impossible, to measure directly the ionising effect of the rays in the irradiated area by means of apparatus in which the ionisation chamber is fixed to the measuring instrument. SIEVERT solved this problem in 1926 in the same

way that Alexander cut the Gordian knot. By means of a genial construction he separated the ionisation chamber from the measuring instrument. His ionisation chamber, which is provided with a condenser, and is constructed in varying sizes and shapes according to the purpose for which it is intended, is entirely detached from the measuring instrument (an electrometer) during radiation, and is attached to it only after radiation. In 1931, he went a step further and separated the chamber from the charging battery also, making the condenser chamber quite independent of any connection during irradiation. Only many years after his invention did he find out that a construction which was the same in principle as his first design had earlier (1925) been used by HALLEDAUER for a specific purpose.

SIEVERT saw the whole range of his »condenser chamber method» and worked it out in detail, constructed a large number of different models and adapted them to widely varying fields, thus opening up new possibilities for research in many instances. For example, small, light and strong condenser chambers can be placed in the cavities of the body or inserted directly into the tissues of the patient whilst measuring the radiation. Since the chambers are relatively cheap in relation to the electrometers, and a large number of chambers can be read off in succession on the same electrometer, the method is ideal for routine measurements, which have for many years been carried out on a large scale in hospitals in Sweden and other countries. The measurement of the distribution of the intensity of the rays in water phantoms can be made advantageously with condenser chambers. The method also presents many advantages in the measurement of protection against radiation, in that it is possible to examine in detail the dose which reaches various parts of the body of radiological workers. Since the chambers are well insulated, it is possible to send them by post for taking measurements in other places. Measurement by post has thus been used in order to compare the dosage in teleradium apparatus in Stockholm and New York.

SIEVERT has also designed highly sensitive instruments for the measurement of radium preparations, based on the condenser chamber principle, and the instruments used for circulating dosage control in radiological departments in Sweden are based on the same principle.

The papers published by SIEVERT are in the field of medical radiation physics as well as in those of radiotherapy and radiobiology.

He has, in a series of publications, investigated the already existing units for roentgen and radium dosage, and has expounded his own suggestions — which have aroused a great deal of attention — for units of measurement. He has examined, both theoretically and experimentally, the distribution of the intensity of the primary gamma-rays in the vicinity of apparatus for radium treatment, and has developed formulas for the

distribution of intensity in various cases occurring in practice, with tables for the functions occurring in the formulas.

SIEVERT has, partly in collaboration with BENNER, demonstrated the importance of secondary rays in radium therapy, and developed certain formulas for the intensity of the secondary rays under various conditions. His theory has been verified experimentally by means of the »radium compensator». In this work he has shown that substances with a medium atomic number constitute the best filter material for secondary beta-radiation, a fact which has long been overlooked. Together with BENNER and OLSSON, he has described the methods and the instruments worked out by him personally, and used in his institute for testing and measuring radium preparations.

The question of protection against injury by radiation has been the object of SIEVERT's unfailing interest. He has shown in particular the dangers of secondary radiation, and has proposed protective measures. His »condenser chamber method» has enabled him to examine the ray doses which reach the roentgen workers. His publication, in collaboration with THORÆUS, on the protective value of various materials, expressed in terms of their lead equivalent, is of great practical value in the erection and equipment of premises for radiological work.

SIEVERT has described his »condenser chamber method» in detail, and has shown its manifold use for measuring and dosage in radiation therapy, and in the control of protection against radiation. He has also adapted this method to several other fields of radiation physics. He has, for instance, measured the absorption of gamma-rays in various materials and the ionisation in various gases as a function of the pressure, the radiation intensity being kept constant. He has also adapted his method to measure the natural radiation in different places, and has described an interesting arrangement for measuring cosmic radiation with the condenser chamber at great depths of water.

SIEVERT's suggestions for methods of roentgen micro-photography are on the border-line between physics and biology, and they appear to open up fresh possibilities for a new micro-analytic method.

SIEVERT and his school have laid the foundations of the development of radiation therapy at Radiumhemmet. SIEVERT's measuring apparatus and his methods for measuring and dosage, as well as the control exercised by his institute over the arrangements for therapy and protection against radiation, have been a steady physical rampart to us in our work. The inspiring discussions with SIEVERT and his colleagues on ways and means in our daily work and in clinical research have resulted in many valuable suggestions.

SIEVERT has, in addition, through his own experimental and theoretical research, wrestled with success with fundamental problems of radiobio-

logy. He has, for example, studied with great interest the »time factor» in radiation therapy, viz. the question of the most suitable relation between the time of irradiation and the intensity of the rays. SIEVERT and FORSSBERG succeeded, by means of apparatus especially designed for this purpose, in dosing and measuring the quantity of rays applied to the fraction of a second, and have thus made it possible to examine the dependence of the radio-sensitivity on the rate of the cell-division rhythm.

Some of SIEVERT's publications have increased to a considerable degree our knowledge of the biological effect of the »natural gamma-radiation» and of the »cosmic radiation». Amongst others, EUGSTER and HAUPTMANN in HESS' laboratory had stated earlier that they had found that germinating seeds, etc., which are allowed to develop cut off from the gamma and cosmic rays show a growth rate which differs from that of cultures living under normal circumstances.

SIEVERT succeeded, by means of an experimental construction of unique precision, in avoiding the sources of error in the majority of earlier and later investigations in this field, and showed that the weak natural rays, both terrestrial and cosmic, have a biological effect. He succeeded, for instance, in showing a retardation of the development by one day in a normal development period of approximately two weeks in the Drosophila — from the newly-laid egg to the newly-hatched fly — when the total ionisation was reduced from ~ 12 to ~ 4—6 ions per cm^3 and second.

The last research work on which SIEVERT was engaged before the War was a theoretical treatment of certain radiobiological questions. He attempted, on the basis of the fact established by many research workers that the biological reactions — especially in the case of weak radiation doses — often have a periodical course, to develop a mathematical formulation of these reactions from the starting-point of generally established facts of physico-chemical nature. These experiments led to the development of differential equations, which have shown themselves capable of rendering correctly in principle a number of facts established by experiment. SIEVERT points out, however, that his theory does not, at present, permit of any opinion on the nature of the biological radiation reactions, but only on their formal and quantitative course.

VAN DER WERFF, the Dutch physicist, has successfully elaborated SIEVERT's principle theoretically, and has applied it to some radiological problems, as, for example, the moment of appearance of erythema after irradiation, and the biological reaction when a total dose is divided into several partial doses. The results of A. FORSSBERG's investigation of the growth reactions of the *Phycomyces Blakesleeanus* after roentgen and gamma-radiation, tally extremely well with SIEVERT's theory.

Constant co-operation with a radiation physicist is a great advantage for a radiotherapeutic clinic, but, on the other hand, it has its disadvan-

tages. The radiation therapeutist, who was formerly forced to strain himself to the utmost to become intimate with the physical demands of dosage and use of the roentgen tubes, is easily tempted into yielding the responsibility of the technical side to the radiation physicist and the trained roentgen technician. A necessary complement to the radiophysical department of a radiotherapeutic clinic is regular instruction in radiation physics and radiation technique for the medical staff and the research workers of the clinic. SIEVERT soon came to this conclusion, and even during his first years as a »voluntary and unpaid collaborator» of Radiumhemmet, he gave demonstrations in radiophysics which were open to all those working there. Since his appointment as Head of the Radiophysical Institute, he has given regular instruction, partly in the form of demonstrations and exercises in measuring and dosage technique, and partly in the form of lectures, with discussions of current problems of medical radiation physics. In 1932, SIEVERT was appointed Associate Professor of Physics at University College, Stockholm, and after Radiumhemmet and its scientific auxiliary institutes had been incorporated with the University Hospital, he was appointed, in 1941, Professor of Radiation Physics at Karolinska Institutet (Stockholm's Medical School). SIEVERT's teaching takes the same form now as formerly, and is given at the radiophysical institute, with the assistance of the heads of the various departments.

SIEVERT's wealth of ideas and organizing ability have not been directed towards scientific problems alone. Parallel to his research work, he has constantly endeavoured to make the result of his research bear fruit in practical application in medicine. His talent for organization first made itself felt in the development of the radiophysical institute and in his co-operation with the radiotherapeutic clinic, and finally found its expression in the creation of a nation-wide organization which was to give the direct support of radiophysical experts to all radiological work in Sweden.

It soon became manifest that the realization of a precise physically standardized dosage and a control of the instruments and roentgen tubes of Radiumhemmet brought considerable advantages, especially in the increased accuracy in the reproduction of various doses, a thorough control of protective measures, and a great saving of time. SIEVERT immediately started an investigation into the needs and possibility of giving radiophysical assistance to all the radiotherapeutic departments of the country. A comparative investigation made in the majority of the hospitals of the size of the »erythema dose» showed that the difference between nominally equal doses was, in reality, very great. On the basis of this investigation, a standard erythema dose was fixed, which later formed one of the cornerstones of the physical standardization of roentgen therapy in Sweden.

It was obviously desirable, in order to facilitate discussion and communication between the radiologists all over the country, to introduce a common physical standardization of the dosage and the running conditions of the roentgen tubes, so that the radiotherapeutic departments could all work according to the same system of measurement.

The Cancer Society decided, at the suggestion of SIEVERT, to attach a »circulating physical department for standardizing roentgen radiation in therapy» to the physical laboratory of Radiumhemmet as from May 1st., 1926. This was to be at the disposal of all the Swedish hospitals which gave roentgen therapy under competent leadership. By means of periodical visits with suitable portable instruments, it was to control the high-tension instruments and roentgen tubes, and to introduce and maintain a physically standardized dosage.

As long ago as 1925, Radiumhemmet's physical laboratory was open for the examination and measurement of radium preparations from other institutes. This work was gradually expanded into a regular control of the larger stocks of radium in all the hospitals of the country.

»The circulating measuring department» was, financially and administratively, entirely independent, but it was housed in the physical laboratory, and had the right to use its instruments. The special equipment for this »physical ambulance» was paid for »privately», and the costs of its upkeep were covered by agreed contributions from the hospitals belonging to the organization. The rapidly increasing number of hospitals which voluntarily availed themselves of this help showed that the »circulating measuring department» filled a generally felt need. In 1926, 9 radiotherapeutic departments had recourse to it, in 1927, 17; in 1930, 33; in 1935, 46, and in 1940, 53, or practically all the departments of radiation therapy in the country.

The success of the control of radiation therapy by the radiophysical institute had aroused a desire in Swedish radiologists for the institute to extend its control to embrace roentgen diagnostics. The Government was approached by representatives for medical and technical radiology on this matter. Since roentgen radiation had become more and more generally used in medicine, dentistry, science, and technology, and at the same time the radiation intensity used was rapidly increasing, the risk for roentgen workers — in Sweden about 4,000 persons — had increased correspondingly. It was, however, only when the circulating measuring department of the radiophysical institute had been created by SIEVERT, that possibilities lay open for a permanent and nation-wide organization for the control of instruments and protective arrangements in all radiological work in Sweden.

At the suggestion of the Committee for Scientific Co-operation of the Jubilee Clinic, the Board of Directors of King Gustaf V's Jubilee Founda-

tion and the directors of the Cancer Society brought forward a proposal for official supervision of all radiological work throughout the country in connection with the taking over by the State of the radiophysical institute. A proposal made by SIEVERT on behalf of Riksförsäkringsanstalten (The State Industrial Insurance Board) and Medicinalstyrelsen (The Medical Board) for advice and instructions for the prevention of accidents and sickness in radiological work formed the basis for the »Law regarding the supervision of radiological work, etc.» which was passed by the Diet of 1941. (*Svensk författningssamling Nos. 334 and 335, 1941, och No. 267, 1945*) as well as for the instructions enforced by Royal Decree for the radiophysical institute, in so far as it concerns the institute's work in the supervision of radiological work, etc. (*Samling av författningar och cirkulär m. m. angående Medicinalväsendet, Ser. A. No. 136, 1941; No. 122, 1942 and No. 108, 1945*).

Since that time, SIEVERT has been the vital force in the development of the radiophysical institute in the expansion of its control activities, and for the practical arrangements necessary for supervision of all the institutes in the country for medical, veterinary-medical and dental roentgen diagnostics, roentgen examinations for technical and scientific purposes, as well as radium therapy and work with radioactive substances in general. The fact that this supervision of the work of all these institutions has taken place with only very slight friction, and that it has progressed for five years to the satisfaction of all concerned, bears good witness to his powers of organization. It is a fact that SIEVERT's organizing ability has contributed in a decisive manner to increasing precision in measuring technique, and in protection measures, and has brought about a standardization of working conditions and a unification of dosage which is perhaps unparalleled in any other country in the world.

During the war years, SIEVERT devoted all his energy into uniting Swedish physicists in carrying out joint work in the service of defence. In 1941, a National Committee for Physics was formed on his initiative. Its activities resulted in the establishment of an institute for Military Physics, of which SIEVERT was the driving force.

SIEVERT has been the Secretary of the Cancer Society of Stockholm since 1945, and in the same year he was elected a member of the Royal Academy of Sciences (Kungl. Vetenskapsakademien) of Stockholm.

SIEVERT's activities are inspired by a personality saturated with originality and energy. He possesses to a high degree the gift of transmitting his enthusiasm to his pupils and his co-workers, and of spurring them on to attack difficult and vital problems. He is one of those people who find repose in working intensively by turns in widely differing fields. His too is the capacity for absolute periodical relaxation.

The confidence which he has inspired in private persons and public institutions through his wealth of ideas, capacity for work and devotion to his tasks have made it possible for him to obtain official support to carry out extensive organizing work.

ROLF SIEVERT has two homes: his home in Stockholm, housed in the same building as his institute and library, and his country home in his much-loved Tvartorp, which he himself manages and where, in the fields and woods, he finds new sources of energy to enable him to wrestle with the joint problems of physics and medicine.

In his family circle, with his truefast and charming wife, with his many fine children, and amongst his friends, he is a never-failing source of joy, brimming over with ideas which lead to many an interesting and entertaining discussion. His favourite hobby is music, and here the organ is his instrument par excellence.

SIEVERT's interest for his fellow-workers in all lands has made him an active member of the International Congresses of Radiology. At the 1928 Congress in Stockholm, he was a member of the Managing Board and of the Organizing Committee, and President of the Section of Radiophysics and Medical Electrology. He is a member since 1928 of »The International X-Ray Unit Committee» and of »The International X-ray and Radium Protection Committee».

At the 4th International Congress in 1934, he gave, on invitation, the chief report on »The hard Gamma-radiation and the penetrating Radiation of terrestrial and cosmic origin», and in 1939 he was invited to read a report at a conference on Measuring of Ionising Rays, arranged by the League of Nations.

Through his work for medical radiophysics and his participation in the international teamwork for the propagation of radiology, ROLF SIEVERT has gained a reputation as one of the pioneers of medical radiophysics.

Swedish physicists and medical men in the service of radiology have united in celebrating ROLF SIEVERT's fiftieth birthday by the publication of this anniversary volume in his honour. In this way he has once more been the inspiration for research work, and yet once more has his name been a signal for Swedish workers in the science of radiation to foregather.

This volume is also a heartfelt tribute from his many friends to a generous and steadfast comrade.

We offer him our thanks for his inspiring energy in our scientific work and for the strong current of friendship and encouragement which has emanated from him.

Now that ROLF SIEVERT has been restored to radiation physics after the years of war, his mind is brimming over with plans to make its latest discoveries bear fruit for radiotherapy, and to develop the co-operation

between physics and radiotherapy into an organized co-operation between all the branches of research in physics and medicine.

The best wish we can offer him on this his fiftieth birthday is that his intellect and his enthusiasm may continue to flourish with undiminished strength, and that his institute may find that support it so well deserves in order that his ideas and his work may bear fruit for science and for medicine.

GÖSTA FORSSELL.

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FROM RADIUMHEMMET, STOCKHOLM (CHIEF: PROF. ELIS BERVEN) AND THE ROENTGEN THERAPY DEPARTMENT OF SÖDERSJUKHUSET, STOCKHOLM (CHIEF: DR. HUGO AHLBOM)

POINTS REGARDING THE »TIME FACTOR» IN ROENTGEN IRRADIATION WITH DIVIDED DOSAGE[1]

by

Hugo Ahlbom

This short paper has two aims, firstly, to draw attention to a recent scientific work on the »time factor» in radiation with divided dosage, and secondly, to discuss a couple of theoretic points connected with this subject.

In May 1944 STRANDQVIST published a book[2] called »Studien über die kumulative Wirkung der Roentgenstrahlen bei Fraktionierung. Erfahrungen aus dem Radiumhemmet an 280 Haut- and Lippen-Karzinomen.» His work covers a period of eight years. The reason why so few cases were treated with roentgen rays during this relatively long period of time was that the routine method of the clinic for such carcinomas is implantation with radium needles. STRANDQVIST's series has been treated experimentally to a certain extent for the purpose of studying and comparing different types of fractioned radiation, the results being judged from the biologic effect on the skin and the therapeutic effect on the carcinomas.

The cases were very thoroughly examined and are described in detail. They were also treated and followed up with unusual care. STRANDQVIST has thus collected an extremely suitable material for dosage and »time-factor» studies.

Favoured with the opportunity to follow closely the whole investigation, I have been much impressed both by STRANDQVIST's ingenious scientific methods and by the theoretic and practical importance of his conclusions and results. I am convinced that in the future they will provide great help and stimulation to radiotherapeutists in all countries. Unfortunately the book came out during the war, and it has only been translated from Swedish into German. It is therefore probably little

[1] Submitted for publication, Dec. 20, 1945.

[2] Acta Radiologica, Suppl. LV, 1944.

known outside the Scandinavian countries, and I have felt it my duty to try to draw the attention of English speaking radiotherapeutists, in particular, to the book.

Figure 1 shows a diagram taken from STRANDQVIST's work. It explains, better than many words I hope, one of the most important results to which the investigation has led. The diagram might be called an iso-effect

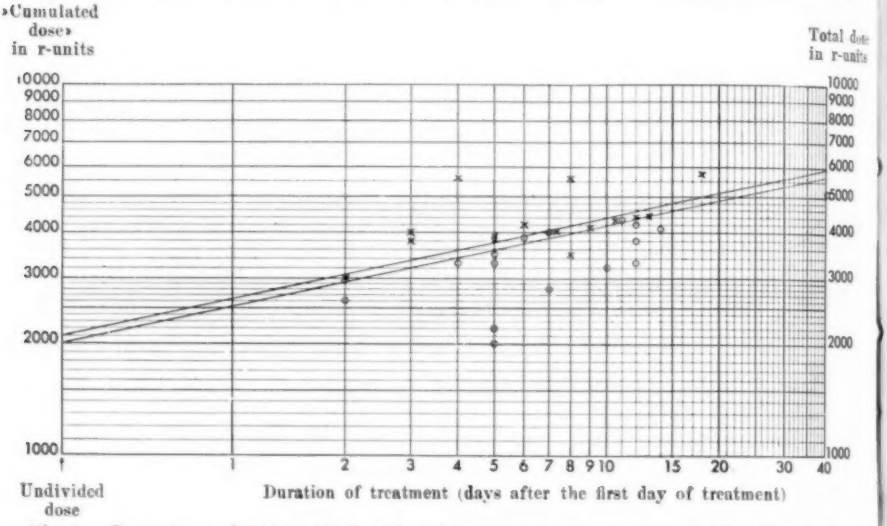

Fig 1. Cases treated 1933—1937 with subsequent recurrence or complication. Recurrence marked with a little circle, complication with a cross.

curve and is the result of plotting the total dosage of cases that had the treatment distributed over a varying number of days. The cured carcinoma cases which had severe reaction or even late skin necrosis, and thus must have received an overdosage, are practically all to be found *above* the upper oblique line of the diagram. Those cases, on the other hand, which received an underdose and consequently showed recurrence of cancer, are practically all collected *below* the lower line. It is quite obvious that the »area of optimal dosage» will be found between the two lines. In this particular diagram, however, only the less satisfactory cases are included for the sake of clearness.

The following statements are made to illustrate the practical application of diagrams of this kind: A good result in superficial squamous cell carcinoma can be expected from a total dosage of 3,400 r (including secondary radiation) given in 72 hours (= 4 daily doses of 850 r). The same good result and the same skin reaction should also follow a total dosage

of about 4,200 r during 6 consecutive days (= 6 × 700 r) or of 5,000 r during 20 days (= 20 × 250 r). A recurrence is very likely to follow a treatment of 3,000 r divided over 10 days (= 10 × 300 r). The risk of necrosis must be considered if a dosage of 4,800 r is distributed over 8 days (= 8 × 600 r).

It is obvious that diagrams of this kind will make it possible to »translate» any given type of fractioned roentgen ray treatment into another type, and also into a »massive» — or undivided — dose with a similar biologic effect. The radiotherapeutist will have much better possibilities

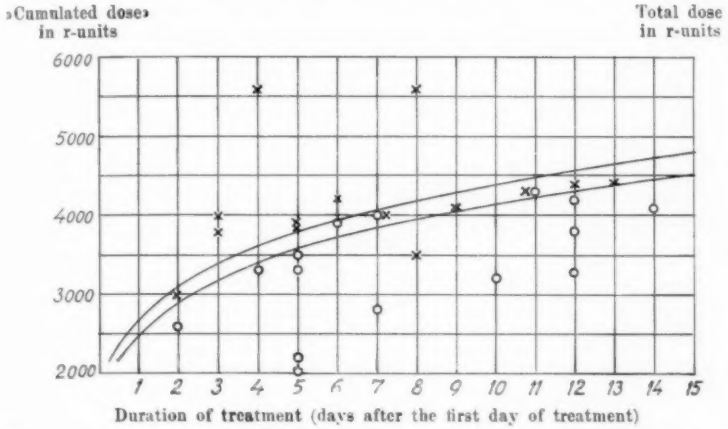

Fig. 2. Cases treated 1933—1937 with subsequent recurrence or complication. Recurrence marked with a little circle, complication with a cross.

to understand and estimate descriptions of radiation methods in the literature, and so on.

Figure 2 shows another of STRANDQVIST's many diagrams, where the »iso-effect curve» has been drawn in an ordinary coordinate system. (In the diagram of figure 1 the double logarithmic system is used.) The curve shows the general shape of a parabola (and correspondingly seems to form a straight line in the double logarithmic coordinate system). STRANDQVIST reminds the reader of the fact that the general rising of the curve depends on the incomplete cumulative effect of the irradiation. If one assumes the cumulation to be complete, the curve would form a horizontal line, because a certain dosage would give the same biologic effect whether given, for instance, over two days or over twenty days. On the other hand, if there were not any cumulation, in other words, if the tissues recovered completely, the curve of figure 2 would rise quickly as a straight line. STRANDQVIST concludes (page 223) that the parabolic

shape of the curve must mean that the cumulative effect of the irradiation is less marked with a short total duration of the treatment, e. g., 3—4 days, than in a treatment with long total duration, e. g., 20—30 days. For really long periods of daily irradiations there seems to be a very low rate of tissue recovery (almost complete cumulation).

The fact that the empiric »iso-effect curve» rises more slowly the longer the treatment period lasts can also be expressed in the following simple way: *the influence of the »time factor» in roentgen treatment with divided dosage declines as the duration of the treatment is increased.* This fact, in my opinion, has an important bearing on the theoretical discussion of the so called *Coutard* method (or »protracted fractioned radiation»), which was rather lively a few years before the war. The essential features of this method were relatively small daily doses given over a period of several weeks, and a certain low intensity (about 5 r per minute). The low intensity was supposed to increase the selectivity of radiation or to decrease the radiation damage of the normal connective tissue, etc. Remembering STRANDQVIST's diagram and its indication of decreased »time factor» influence for a treatment lasting several weeks, one is surprised that a lowering of the intensity from 30—50 r to 5 r per minute should mean such a difference in the biologic and therapeutic effect. It must be said, however, that no real proof of the importance of the low intensity has been published. COUTARD's results were remarkable, but *might* have been equally good with the same roentgen doses and »ordinary intensity». In my opinion his good results depended chiefly upon his introduction of really high total tumour doses and upon great personal interest and skill in the actual clinical and therapeutic work. A few authors have published good results with fractioned roentgen treatment *without* »protraction». STRANDQVIST says that the rôle of the protraction in the COUTARD treatment »seems to be overestimated». He also quotes experimental irradiations made by BORAK, HOLTHUSEN, WITTE and KEPP, that seem to support this view. In a publication from 1938[1] COUTARD appears to be less impressed by the low intensity than previously. At least he recommends for laryngeal carcinomas with differentiated cells such high daily doses (500—600 r) that protraction seems impracticable, and he makes no statement as to the intensity he uses for these cases.

The several authors who have expressed the opinion that protraction is unnecessary in treatment with a dosage distributed over several weeks (STRANDQVIST, HOLTHUSEN, WITTE and others), usually admit that an intensity difference amounting to the relation of 1: 8 or 1: 10 in an undivided dose gives a noticeable difference in biologic effect (a more marked effect with the higher intensity). They can give no definite explanation, however, for the fact that there is no such difference in biologic effect when a dosage is divided over two or more weeks. In

[1] Amer. Journ. of Roentg. 40, p. 509.

my opinion the explanation must be the aforementioned decreasing influence, of the »time factor» shown by STRANDQVIST's diagrams.

Following STRANDQVIST's example in discussing the diagrams and their meaning, I have hitherto only mentioned the two »antagonistic» factors, *cumulation* of the radiation and tissue *recovery*. The decrease of the tissue recovery during irradiation lasting several weeks might, of course, partly depend upon another biologic factor, namely a gradual sensibilisation of the tissues during the course of the irradiation. We know from daily clinical experience that human skin in a state of marked roentgen erythema seems more radiosensitive than normal skin. If it were proved that this hyperaemia of the skin increases the cumulative effect of the radiation in the skin, but perhaps not to the same degree in the cancer tissue, the obvious course would be that treatment should be finished *before* erythema of the skin appeared. Even if such proof does not exist and may be difficult to obtain, it should be preferable to give fractioned treatment, if possible, in such daily doses that the total duration of treatment does not exceed three or four weeks. In this way it should often be possible to finish the treatment before the intense skin erythema has had time to develop.

SUMMARY

As a basis for a discussion of certain »time-factor» problems in fractioned roentgen ray therapy, a recent work by STRANDQVIST, done at the Radiumhemmet, Stockholm, is described. The importance of this theoretically very interesting work for practical radiotherapy of malignant tumours is pointed out. An attempt is made to explain in the light of STRANDQVIST's results why protraction seems to be of minor importance when the roentgen dosage is distributed over a relatively long period.

ZUSAMMENFASSUNG

Als Unterlage für eine Erörterung gewisser Zeitfaktor-Probleme bei fraktionierter Röntgentherapie, wird über eine kürzlich von STRANDQVIST aus Radiumhemmet, Stockholm, veröffentlichte Arbeit berichtet. Das theoretische Interesse dieser Arbeit und ihre grosse praktische Bedeutung für die Strahlenbehandlung maligner Tumoren werden betont. Es wird ein Versuch gemacht, an Hand der STRANDQVIST'schen Resultate zu erklären, warum Protrahierung einer über längere Zeit fraktionierten Röntgendosis von geringerer Bedeutung zu sein scheint.

RÉSUMÉ

Un travail récemment paru de STRANDQVIST, provenant du Radiumhemmet, Stockholm, est analysé pour servir de base à la discussion de certains problèmes soulevés par le »facteur-temps» en radiothérapie fractionnée. Mise en évidence de l'intérêt théorique et de la grande importance pratique du dit travail pour le traitement des tumeurs malignes par les radiations. Essai d'expliquer, à la lumière des résultats de STRANDQVIST, pourquoi en traitements fractionnés pendant un temps relativement longue, l'étalement de chaque irradiation ne semble jouer qu'un rôle accessoire.

FROM THE ROYAL INSTITUTE OF TECHNOLOGY, INSTITUTE FOR ELECTRONICS
(HEAD: PROF. H. ALFVÉN)

A NEW TYPE OF WAVE MOTION AND ITS IMPORTANCE IN SOLAR PHYSICS[1]

by

Hannes Alfvén

Several different types of wave motion have long been known: mechanical waves (of different types), electromagnetic waves and material waves. In the present article a new type will be described, provisionally called *magneto-hydrodynamic* waves. These waves may in some measure be conceived as a combination of mechanical (hydrodynamic) and electromagnetic waves, but differ fundamentally from both these types.

The magneto-hydrodynamic wave motion can be derived on a purely theoretical basis (§ 1—5). It has not as yet been demonstrated experimentally on the Earth. It is possible that it could be detected in the laboratory. Such waves may conceivably play a certain part in the ionosphere. Their greatest importance is to be found, however, in solar physics, especially in connection with the theory of the origin of sunspots (§ 6—7).

§ 1. Magneto-Hydrodynamic Waves. Qualitative Discussion

The condition for the occurrence of magneto-hydrodynamic waves is the presence of an electrically conducting liquid (or gas) in a magnetic field.

Let us, for the sake of simplicity, make the initial assumption that the magnetic field is homogeneous and has the strength H_0. We then lay a right-angled coordinate system with the z-axis parallel to the lines of magnetic force. We further assume that at a certain instant t_0 the whole fluid is at rest, with the exception of a pillar, bounded in the x-z-plane by A B C D (Fig. 1) and extending indefinitely in the y-direction. This pillar moves with the velocity v in the direction of the y-axis.

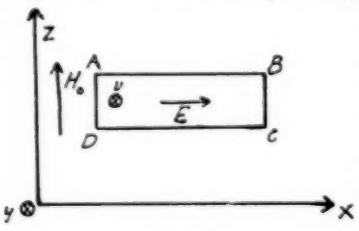

Fig. 1.

[1] Submitted for publication, Febr. 9, 1946.

If a body moves in a magnetic field, it becomes electrically polarized in a direction at right angles to the magnetic field and to the direction of motion. The electrical field thus produced is proportional to the vector product of the magnetic field and the velocity:

$$E = \frac{\mu}{c} v \times H_0 \quad (\mu = \text{permeability}, c = \text{velocity of light}).$$

In our case there consequently arises, in the moving part of the fluid, an electrical field in the positive direction of the x-axis. The electromotive force induced in this manner produces currents, for we have assumed that the fluid is electrically conducting. The currents move in the direction of the induced electrical field within A B C D, and are closed in the surrounding stationary fluid, so that the electrical current system shown in Fig. 2 arises.

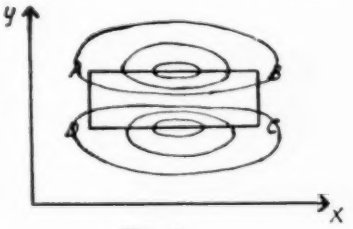

Fig. 2.

An electrical current I, moving in a magnetic field, is acted upon by a force F which is at right angles to the current and to the magnetic field:

$$F = \frac{\mu}{c} I \times H_0$$

As the current in the moving part of the fluid flows in the positive direction of the x-axis, the force is negatively directed along the y-axis, *i. e.* it impedes the movement. In the adjacent parts of the stationary fluid, however, the current flows in the negative direction of the x-axis, which causes the force to take the positive direction of the y-axis, *i. e.* gives an acceleration in the initial direction of movement. The layer of the fluid that was moving in the beginning is thus retarded, and the layers above and below it accelerated. *Thus, the induced current system tends to transfer the initial movement to the surrounding layers.* The result will be that after some time A B C D is at rest, while E F B A and D C G H (see Fig. 3) are moving in the direction of the y-axis. As the same mechanism is still acting, the state of motion will be transmitted in the posi-

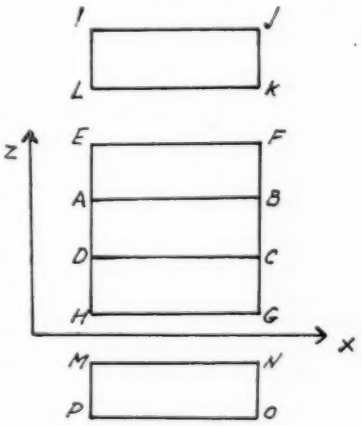

Fig. 3.

tive and negative directions of the z-axis, so that after some time a part I J K L and another M N O P are moving, while the remaining parts of the fluid are at rest.

§ 2. Derivation of the Wave Velocity

In order to formulate the problem mathematically, we must start with Maxwell's equations

$$\text{rot } H = \frac{1}{c}\left(4\pi i + \frac{\partial D}{\partial t}\right) \quad \ldots\ldots\ldots (1)$$

$$\text{rot } E = -\frac{1}{c}\frac{\partial B}{\partial t} \quad \ldots\ldots\ldots (2)$$

combined with

$$B = \mu \cdot H \quad \ldots\ldots\ldots (3)$$

$$i = \sigma\left(E + \frac{v}{c} \times B\right) \quad \ldots\ldots\ldots (4)$$

where σ is the electrical conductivity. As the displacement current is negligible with respect to the conduction current, the second term on the right in (1) can be neglected. We must add to these equations the hydrodynamic equation

$$\varrho \frac{dv}{dt} = \frac{1}{c}(i \times B) - \text{grad } p \quad \ldots\ldots\ldots (5)$$

(ϱ = mass density, p = pressure), the right-hand side of which gives the forces acting acceleratingly upon a unit volume of the fluid. If the fluid is incompressible, which we wish to assume, we also have

$$\text{div } v = 0 \quad \ldots\ldots\ldots (6)$$

In order to obtain a survey of the phenomena, we shall begin with a study of a plane undamped wave in the direction of the z-axis and assume that ϱ and μ are constant and that $\sigma = \infty$. All vectors are then independent of x and y but dependent on z and the time t. According to the equations (1) and (2) and the above-mentioned condition, $i_z = 0$ and $H_z = \text{constant} = H_0$. Furthermore, we may put $v_z = 0$. If we rotate the coordinate system so that $i_y = 0$, we obtain from (1)

$$i_x = -\frac{c}{4\pi}\frac{\partial H_y}{\partial z} \quad \ldots\ldots\ldots (7)$$

$$i_y = i_z = 0$$

$$H_x = \text{constant} = 0$$

$$H_z = H_0 \quad \ldots\ldots\ldots (8)$$

The primary magnetic field H_0 is superimposed by a field $= H_y$, caused by the induced current system i.

We introduce these values into (5). As, according to our assumptions, grad p has no component in the x—y-plane, we obtain

$$\frac{\partial v_x}{\partial t} = 0; \quad v_x = \text{constant} = 0$$

$$\frac{\partial v_y}{\partial t} = \frac{\mu H_0}{4\pi\varrho} \cdot \frac{\partial H_y}{\partial z}; \quad v_z = 0 \quad \ldots\ldots\ldots\ldots (9)$$

and further

$$\frac{\partial p}{\partial z} = -\frac{\mu}{8\pi} \frac{\partial (H_y^2)}{\partial z} \quad \ldots\ldots\ldots\ldots (10)$$

As i is finite, equation (4) gives

$$E = -\mu \frac{v}{c} \times H$$

or combined with (8) and (9)

$$E_x = -\mu \frac{v_y}{c} H_0 \quad \ldots\ldots\ldots\ldots (11)$$

$$E_y = E_z = 0$$

Equation (2) gives

$$\mu \frac{\partial H_y}{\partial t} = -c \frac{\partial E_x}{\partial z} \quad \ldots\ldots\ldots\ldots (12)$$

From (12), (11) and (9) we have

$$\frac{\partial^2 H_y}{\partial t^2} = \frac{\mu H_0^2}{4\pi\varrho} \frac{\partial^2 H_y}{\partial z^2} \quad \ldots\ldots\ldots\ldots (13)$$

This equation is identical with the wave equation and represents a wave moving in the direction of the z-axis with the velocity

$$V = \frac{H_0 \sqrt{\mu}}{\sqrt{4\pi\varrho}} \quad \ldots\ldots\ldots\ldots (14)$$

We have thus derived, from the equations (1)—(6), a wave moving with a velocity proportional to the magnetic field strength and inversely proportional to the mass density of the fluid. The velocity is independent of the frequency as well as of the amplitude.

The increase in the velocity with the magnetic field is due to the fact that both the strength of the induced current and the force produced by a certain current are proportional to the strength of the magnetic field. The decrease in velocity as the density increases, is due to the longer time necessary for the acceleration of a fluid with higher density.

In order to obtain a conception of the wave velocity, we may calculate it, for example, for $H = 100$ gauss, $\varrho = 1$ g/cm³, $\mu = 1$. V is then found to be 28 cm/sec.

In order to determine how the induced magnetic field H_y, the velocity of the fluid v_y, the induced current i_x, the induced electrical field E_x and the pressure p vary in a sine wave, we put

$$H_y = A \sin \omega \left(t - \frac{z}{V}\right) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (15)$$

and obtain

$$v_y = - \frac{A\sqrt{\mu}}{\sqrt{4\pi\vartheta\varrho}} \sin \omega \left(t - \frac{z}{V}\right) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (16)$$

$$i_x = A \frac{c\omega}{H_0} \sqrt{\frac{\varrho\vartheta}{4\pi\mu}} \cos \omega \left(t - \frac{z}{V}\right) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (17)$$

$$E_x = A \frac{H_0\sqrt{\mu^3}}{c\sqrt{4\pi\vartheta\varrho}} \sin \omega \left(t - \frac{z}{V}\right) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (18)$$

$$p = p_0 - \frac{\mu A^2}{8\pi} \sin^2 \omega \left(t - \frac{z}{V}\right) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (19)$$

These quantities are plotted as functions of t and z in Fig. 4 and Fig. 5

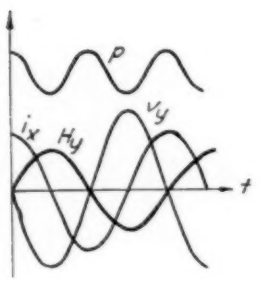

Fig. 4.

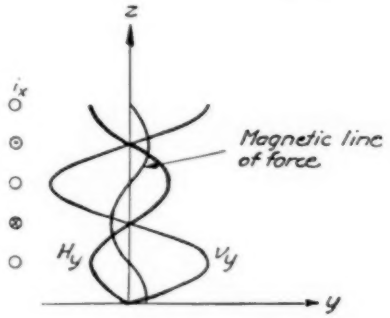

Fig. 5.

The magnetic lines of force, which were originally straight lines

$$x = x_0, \quad y = y_0 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (20)$$

change their form as a consequence of the field H_y superimposed on H_0. As the angular coefficient of the lines of force must everywhere be

$$\frac{dy}{dz} = \frac{H_y}{H_z}$$

we find, by integrating (15), that the lines of force are sine curves with

$$x = x_0$$
$$y = y_0 + \frac{A\sqrt{\mu}}{\omega\sqrt{4\pi\vartheta_\varrho}} \cos\omega\left(t - \frac{z}{V}\right) \quad \ldots\ldots\ldots (21)$$

If we derive (21) with respect to t, we will find that the magnetic lines of force move with the same velocity v_y (in accordance with (16)) as the fluid.

§ 3. Magneto-Hydrodynamic Waves as Oscillations of the Magnetic Lines of Force

A simple picture of the magneto-hydrodynamic wave motion is obtained in the following way. The magnetic lines of force are often regarded as elastic strings. The pondo-motor effects of a magnetic field may be visualized by imagining that such strings attempt to contract and to impose a lateral pressure upon one another. — If a magnetic field exists within a body of infinite conductivity, no change in position of the lines of force can occur, since such a change would give rise to opposing currents, which would be infinitely large as a consequence of the infinite conductivity. The lines of force are thus »frozen» in the body. As we have assumed that the fluid in question has an infinite conductivity, no relative motion between the fluid and the magnetic field is possible. The fluid may be considered as »glued» to the magnetic lines of force, which may accordingly be regarded as material strings with masses equal to the mass of the fluid per line of force. Like ordinary strings, these too may begin to oscillate, and the velocity of the magneto-hydrodynamic waves may actually be derived from the equation for the oscillation of a string, which reads

$$m\frac{\partial^2 y}{\partial t^2} = S\frac{\partial^2 y}{\partial z^2} \quad \ldots\ldots\ldots\ldots (22)$$

(m = mass of string per unit length, S = tension in the string), provided that the string is parallel to the z-axis and oscillates in the direction of the y-axis. A transverse oscillation in such a string has the wave velocity

$$V = \sqrt{\frac{S}{m}} \quad \ldots\ldots\ldots\ldots (23)$$

If we wish to apply these equations to the oscillations of the magnetic lines of force, it is necessary to substitute for S the force with which

a magnetic line of force endeavours to contract. The force per unit area at right angles to the field strength in a magnetic field is

$$P = \frac{1}{8\pi} \mu H^2 \quad \ldots \ldots \ldots \ldots \quad (24)$$

As the number of the lines of force per unit area is H, the tension per line of force will be

$$S = \frac{P}{H} = \frac{1}{8\pi} \mu H \quad \ldots \ldots \ldots \ldots \quad (25)$$

The mass of the string m will be the mass per line of force, *i. e.*

$$m = \frac{\varrho}{H} \quad \ldots \ldots \ldots \ldots \quad (26)$$

If (25) and (26) are substituted in (23), however, a wave velocity is obtained which differs from (14) by a factor $\sqrt{2}$. This is due to the fact that the magnetic lines of force also act upon one another by the above-mentioned lateral pressure. This is most simply allowed for by calculating the expressions for the energies of oscillating strings and lines of force. If the string is deformed from a straight line ($y = y_0$), so that its equation becomes

$$y = f(z), \quad \ldots \ldots \ldots \ldots \quad (27)$$

its length between z and z + dz is increased from dz to $dz \sqrt{1 + \left(\frac{dy}{dz}\right)^2}$. Hence its total increase in length is

$$\int \left[\sqrt{1 + \left(\frac{dy}{dz}\right)^2} - 1 \right] dz \quad \ldots \ldots \ldots \quad (28)$$

The tension in the string being S, this means that the potential energy of the string has increased by

$$W = S \int \left[\sqrt{1 + \left(\frac{dy}{dz}\right)^2} - 1 \right] dz$$

or, if dy/dz is assumed to be $\ll 1$,

$$W = \frac{S}{2} \int \left(\frac{dy}{dz}\right)^2 dz \quad \ldots \ldots \ldots \quad (29)$$

If a magnetic line of force is deformed from a straight line $y = y_0$ with the field strength H_0 to a form corresponding to equation (27), the consequence will be that the field strength also acquires an y-component. As

$$\frac{dy}{dz} = \frac{H_y}{H_z}$$

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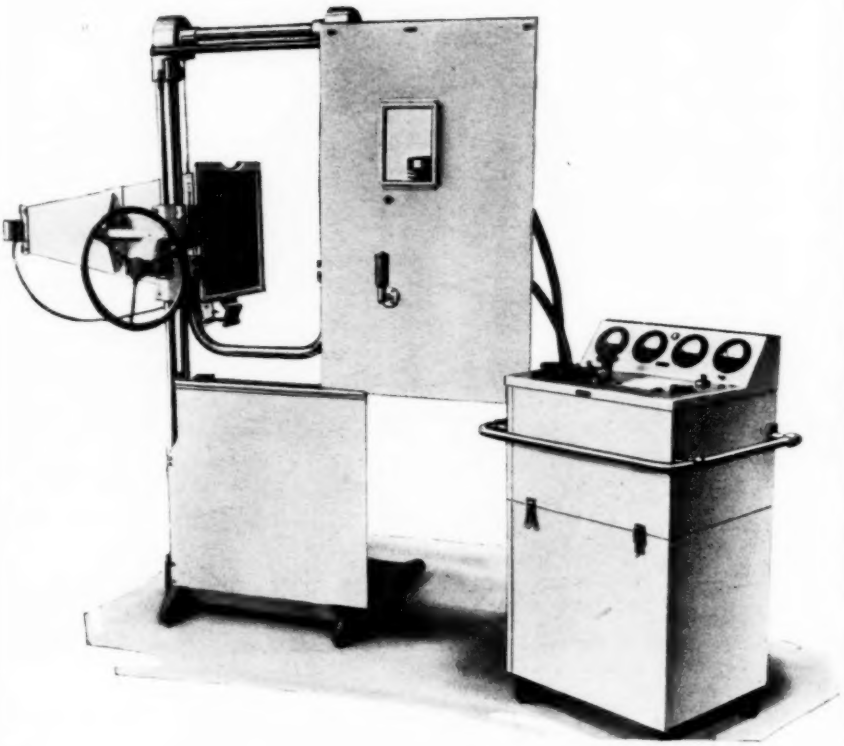

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and H_z is still equal to H_0, we obtain

$$H_y = H_0 \frac{dy}{dz} \quad \ldots\ldots\ldots\ldots (30)$$

The increase in energy due to the superimposing field H_y amounts to $\frac{\mu}{8\pi} \cdot Hy^2$ per unit volume and hence per unit length of a line of force

$$W = \frac{\mu}{8\pi H_0} \int H_y^2 dz = \frac{\mu H_0}{8\pi} \int \left(\frac{dy}{dz}\right)^2 dz \quad \ldots\ldots (31)$$

A comparison between (29) and (31) shows that we should put

$$S = \frac{1}{4\pi} \mu \cdot H_0 \quad \ldots\ldots\ldots\ldots (32)$$

instead of (25). The difference is due to the fact that, in the former case, we have not taken the lateral pressure of the lines of force into consideration. By inserting (26) and (32) in (23) we obtain

$$V = \frac{H_0 \sqrt{\mu}}{\sqrt{4\pi\varrho}}$$

in agreement with (14).

§ 4. Magneto-Hydrodynamic Waves as a Special Case of Electromagnetic Waves

According to what has been said above, it is possible to regard magneto-hydrodynamic waves as oscillations by magnetic lines of force, »materialized» into strings, on to which a conducting fluid has been »glued». This conception gives in many cases a surprisingly good survey of the phenomena. It is, however, also possible to regard the magneto-hydrodynamic waves as an extreme case of electromagnetic waves, in spite of the fact that their velocity, as shown in the example calculated above, may be nine powers of ten lower than the velocity of light. That this is possible is shown by the following consideration:

If an electrically conducting liquid (or gas) is situated in a constant magnetic field H_0, and a homogeneous electrical field E is applied at right angles to the magnetic field, the fluid starts moving at right angles to H_0 and E, owing to the mechanical force of the current produced by the electrical field. The current in the direction of E decreases as the velocity of the fluid increases, since an opposing field

$$E' = \frac{\mu}{c} v \times H_0 \quad \ldots\ldots\ldots\ldots (34)$$

arises. When the velocity of the fluid has reached the value $v = \frac{c}{\mu} \frac{E}{H_0}$, the current becomes zero, since the induced field entirely neutralizes the applied field. A stationary state has then been attained. If the mass density of the fluid be ϱ, the kinetic energy per unit volume is

$$w_k = \frac{\varrho v^2}{2} = \frac{\varrho c^2}{2\mu^2} \cdot \frac{E^2}{H_0^2} \quad \ldots\ldots\ldots\ldots (35)$$

Furthermore, there is, as a consequence of the applied electrostatic field, an electrostatic energy $\frac{1}{8\pi} E^2$, so that the total increase of energy produced by applying the electrical field amounts to

$$w = \left(1 + \frac{4\pi c^2 \varrho}{\mu^2 H_0^2}\right) \frac{E^2}{8\pi} \quad \ldots\ldots\ldots\ldots (36)$$

We may compare this process with the charging of a condenser, in the dielectric of which an electrical field E produces an increase of energy

$$W = \varepsilon \frac{E^2}{8\pi} \quad \ldots\ldots\ldots\ldots (37)$$

On comparing the two expressions (36) and (37), we find that the energy that has to be supplied to a conducting fluid in a magnetic field in order that a stationary state shall be attained with an electrical field E, is equal to that for a dielectric with the dielectric constant

$$\varepsilon = 1 + \frac{4\pi c^2 \varrho}{\mu^2 H_0^2} \quad \ldots\ldots\ldots\ldots (38)$$

In a medium with the dielectric constant ε and the permeability μ, an electromagnetic wave is transmitted with the velocity

$$V = \frac{c}{\sqrt{\varepsilon \mu}} \quad \ldots\ldots\ldots\ldots (39)$$

If the value of the dielectric constant is introduced into this expression, we obtain

$$V = \frac{c}{\sqrt{\mu \left(1 + \frac{4\pi c^2 \varrho}{\mu^2 H_0^2}\right)}} \quad \ldots\ldots\ldots\ldots (40)$$

or, of $4\pi c^2 \varrho \gg H_0^2$, approximately

$$V = \frac{H_0 \sqrt{\mu}}{\sqrt{4\pi \varrho}} \quad \ldots\ldots\ldots\ldots (41)$$

which is the same velocity as was earlier deduced. The difference between (40) and the previously derived velocity is due to the fact that, in the

deduction of (14), the dielectric displacement current was neglected in relation to the conduction current.

The values for the dielectric constant obtained from (38) are naturally very high. For a velocity $V = 30$ cm/sec., the dielectric constant is

$$\varepsilon = 10^{18}$$

Thus, a conducting fluid in a magnetic field has the same properties for waves in the direction of the magnetic field, as in a dielectric with an extremely high dielectric constant. The fluid is strongly anisotropic. Waves in another direction are damped very rapidly, in accordance with the usual laws for the propagation of electromagnetic waves in conductors.

§ 5. Magneto-Hydrodynamic Rings

In the foregoing discussion we have treated a simple special case, that of plane, damped waves. The general solution of the problem has been given by C. WALÉN. He has shown that if a motion occurs in a conducting fluid in a magnetic field, the state of motion is displaced parallel and anti-parallel to the magnetic field. Of special interest is his treatment of the case where, in a fluid otherwise at rest, waves are excited by the setting in motion of a ring-formed element (see Fig. 6). In an incompressible fluid where each motion must take place along a closed curve, this can be considered as the fundamental type of motion. WALÉN has shown that if a ring is set in motion with, for example, the velocity 2 v, it divides into two rings, each with the velocity v, which move apart one in the direction of the magnetic field and the other in the reverse direction. The migration velocity is $\pm V$, where V is the velocity of the magneto-hydrodynamic waves, given by eq. (14).

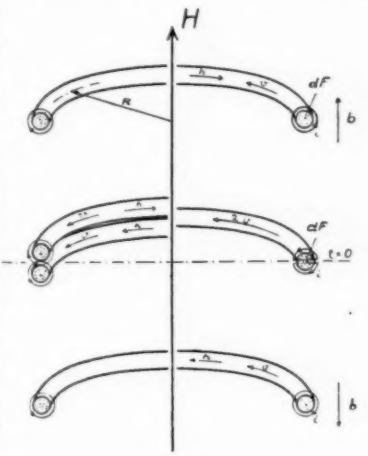

Fig. 6.

Each ring has the characteristic that within its torus surface the fluid has a certain velocity v, and that within the same surface the prevailing magnetic field H_0 has superimposed upon it an induced magnetic field

$$H' = v \frac{H_0}{V}$$

This field is produced by currents moving in the bounding surface of the ring. The centrifugal force produced by v, is exactly compensated by the contracting force exerted by the magnetic field of the ring. This explains why the ring can pass through the fluid without disturbing the parts lying outside (or within) it.

WALÉN, when treating the case where the fluid has finite electrical conductivity, finds that this property involves an increase in the cross-section of the ring with time, simultaneously as the magnitudes of v and H′ decrease. The state of motion and the magnetic field in the ring diffuse out, so to say, into the surroundings, at the same time as the ring progresses through the fluid.

§ 6. On the Origin of Sunspots

The wave-motion studied here appears to be of interest in connection with the problem of the origin of the sunspots.

Sunspots are dark areas on the surface of the Sun where the temperature is approx. 1,000° lower than normal. They have been conceived as enormous vortices, a counterpart to the atmospheric cyclones on the Earth. By the vortical motion a pressure fall would be produced, which, by adiabatic cooling, would bring about a reduction in temperature. Evidence against this suppostition, however, is provided by the fact that the motions within and around the sunspots are rather in a radial than in a tangential direction. Furthermore, the frequently somewhat irregular structure of a sunspot is scarcely such as to give the impression of a vortex.

Great significance attaches to HALE's discovery that the sunspots always possess very strong magnetic fields. The light from a sunspot shows a Zeeman effect, often indicating a field strength of several thousand gauss. Sunspots normally appear in pairs; it proves that, if one member of the pair is a magnetic north pole, the other is a magnetic south pole.

If it be assumed that a sunspot is a magnetic vortex, the appearance of the magnetic field is difficult to understand. For a vortex to develop a magnetic field, it is essential that the rotating matter is electrically charged, so that a circulating current is produced. In order to explain fields of the strengths observed, however, a charge is required that is many powers of ten higher than can reasonably be supposed in this case. Thus, even if a sunspot be a vortex, the appearance of the magnetic field cannot be explained.

It therefore appears simpler to postulate the magnetic field and to investigate whether such field can explain the other properties of a sunspot. Such a viewpoint is justified by the fact that a sunspot has never been observed without a magnetic field. If we assume that in an electric

ally conducting atmosphere there is a magnetic field of strength H, it can readily be shown that we must consequently add to other pressures (gaseous pressure, radiation pressure) the magnetostatic pressure

$$p = \frac{\mu}{8\pi} H^2$$

This pressure may be considered to arise from the reciprocal action between the magnetic field and the electrical currents necessary to maintain this field.

For equilibrium in the atmosphere, it is required that the resultant pressure at a certain level have a certain value. The existance of the magnetostatic pressure in a sunspot therefore involves a reduction in the gaseous pressure by the same amount, which brings about a cooling. The pressure drop in the magnetic field concerned here will amount to some tenths of an atmosphere. In the layers of the solar atmosphere where the sunspot phenomenon manifests itself, this is a very considerable change in pressure. Although a detailed investigation of these relationships has not yet been made, it appears probable that, by assuming the magnetic field to be primary, it will be possible to explain the other properties of a sunspot as produced by this field.

§ 7. Magneto-Hydrodynamic Wawes on the Sun.

It still remains to explain the origin of the magnetic field which, according to the above considerations, gives rise to the sunspots. The search for its origin in phenomena near the Sun's surface, proves to be fruitless. The introduction of the magneto-hydrodynamic waves, however, brings with it the possibility that the field is produced deep in the Sun's interior and is transported out to the surface in the form of such a wave. Actually the astronomers have to assume, in view of the theory of energy production (by nuclear reactions) in the Sun's centre, that the solar core is in a state of turbulence. As the Sun has a general magnetic field which probably has about the same character as that of the Earth (in the first approximation a dipole field), a vortex in the Sun's core must give rise to magneto-hydrodynamic waves, which move outwards to the surface along the lines of force of the general field.

As the density distribution in the Sun's interior is quite well known, it is possible from (14) to calculate the wave velocity, provided that the magnetic field is also known. It is most simple to suppose that the field is a dipole field arising from a magnetic dipole in the Sun's centre. Let us assume further, that, at a certain instant, a series of vortex rings is generated in the Sun's centre. These migrate outwards along the lines of force, the form of which is shown in Fig. 7. After about 10^9 seconds

(30 years) they arrive at the solar surface. A calculation shows that they first reach the surface at high latitudes and only arrive later in the vicinity of the equator. (The successive positions of the wave-front, according to calculations by WALÉN, are shown in Fig. 7.)

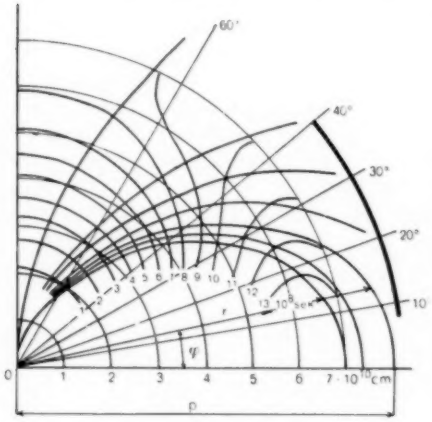

Fig. 7.

This reasoning is concordant with certain observational facts. The number of the sunspots varies periodically, so that the maximum is reached every eleventh year. At the beginning of a sunspot period, the first spots are seen at high latitudes (approx. 30° N and S). The two areas in which the spots appear, then move towards the equator. The final spots in a period lie near the equator, and the next period begins simultaneously with a fresh series of spots at 30°.

If all the spots in a period originate from vortices developed at about the same time in the central regions of the Sun, this phenomenon is explicable. According to the above calculations, the vortices will first reach the surface at high latitudes, for which reason the spots must first appear there. The migration of the wave-front towards the equator hence corresponds to the displacement of the sunspot zones to lower latitudes.

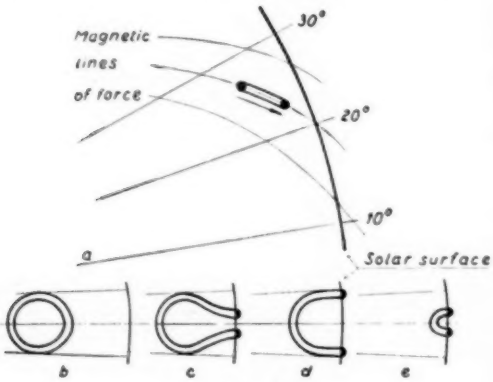

Fig. 8.

The appearance of the sunspots in pairs can also be explained, if magneto-hydrodynamic rings of the type discussed in § 5 are produced in the Sun's centre. When such a ring reaches the solar surface, strong magnetic fields will arise at both points of intersection between the ring and the surface. These fields will produce a fall in pressure, which in turn will give rise to sunspots. It immediately follows from the magnetic properties of the ring that, if one spot is a

magnetic north pole, the other must be a magnetic south pole. While the ring migrates up through the surface, the distance between the two intersection points will vary. In the beginning it will be small, increase to a maximum (equal to the diameter of the ring) and then decrease (cf. Fig. 8). A bipolar sunspot actually is developed in such a way that the distance between its two components at first is small and rapidly increasing to a maximum. It can also be observed, at least in large spots, that the two components finally commence to reapproach one another before the spots are dispersed.

One of the most important problems regarding sunspots is naturally presented by the eleven-year period. It would take us too far to enter here upon the rather involved discussion of this matter. It proves, however, that it is necessary to assume that the vortices are not developed exactly in the centre (as we have supposed here), but in two regions of activity, one northerly and one southerly, lying in the core of the Sun but at some distance apart. The length of the sunspot period is presumably determined by the fact that the time required by the waves to pass from one activity region to the other is about 11 years. The periodicity arises in a kind of relaxation oscillation in which both activity regions partake. This view is supported by an empirically demonstrable correlation between the sunspot distributions on the northern and southern hemispheres.

SUMMARY

In an electrically conducting liquid in a magnetic field the interaction between mechanical and electromagnetic phenomena produces a type of wave motion, called magneto-hydrodynamic waves. These waves have not as yet been discovered on the Earth but they are likely to be of importance in solar physics, especially for the theory of sunspots.

In connection with the generation of the solar energy in the central parts of the sun whirls are produced which by means of magneto-hydrodynamic waves travel to the solar surface where they manifest themselves as sunspots.

ZUSAMMENFASSUNG

In einer elektrisch leitenden Flüssigkeit in einem magnetischen Feld kann die Wechselwirkung zwischen mechanischen und elektromagnetischen Kräften eine Art von Wellenbewegung hervorrufen die magneto-hydrodynamische Wellen genannt wird. Diese Wellen sind noch nicht auf der Erde nachgewiesen, aber sie sind in der Physik der Sonne von Bedeutung, insbesondere für die Erklärung der Sonnenflecke.

Bei der Erzeugung der Sonnenenergie in den inneren Teilen der Sonne werden Wirbel erzeugt die als magneto-hydrodynamische Wellen bis zur Sonnenoberfläche fortgepflantzt werden, wo sie als Sonnenflecken sichtbar werden.

RÉSUMÉ

Dans un liquide conducteur de l'électricité, à l'intérieur d'un champ magnétique, l'interaction entre les phénomènes mécaniques et électromagnétiques produit un type de mouvement ondulatoire appelé ondes magnéto-hydrodynamiques. Ces ondes n'ont pas encore été observées sur la terre mais elles ont une importance dans la physique solaire spécialement en ce qui concerne l'explication des taches solaires.

La genèse de l'énergie solaire dans l'intérieur du soleil donne lieu à la formation de tourbillons qui sont transmis par l'intermédiaire d'ondes magnéto-hydrodynamiques à la surface du soleil où ils deviennent visibles sous l'aspect de taches solaires.

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FROM THE RADIOPHYSICAL INSTITUTE (CHIEF: PROF. R. SIEVERT)

AN INSTRUMENT FOR CALCULATING ROENTGEN RAY DOSES FROM CONDENSER CHAMBER READINGS[1]

by

Sven Benner

At the Radiophysical Institute, a large number of routine measurements of roentgen doses have long been made on patients receiving treatment at Radiumhemmet. For this purpose, condenser chambers according to SIEVERT (1) are used. In recent years, doses have been measured in about 6,000 treatments a year. As two chambers are usually applied for each measurement in order to increase the reliability of the values found, the aggregate number of readings has been about 12,000 a year. This has necessitated careful planning of the work so as to attain the greatest possible number of measurements per person engaged on this work.

One of the measures taken for this purpose was to design an instrument simplifying the calculation of roentgen dose from the reading of the loss of charge in a condenser chamber. The dose is found by the formula

$$D = kd \cdot \frac{760}{b} \cdot \frac{273 + t}{293} = kdc \quad \ldots\ldots\ldots (1)$$

where D is the roentgen dose and k a constant characteristic of each chamber and radiation quality. This constant is equal to the number of r needed to decrease the condenser chamber potential by 1 V at 20° C and 760 mm pressure. d is the loss of potential observed. The factor $c = \frac{760}{b} \cdot \frac{273 + t}{293}$, where b is the atmospheric pressure and t the temperature of the chamber during the irradiation, reduces the value of d to 20°C and 760 mm pressure, viz. the standard conditions for which the constant k has previously been determined. This correction factor has been tabulated for all b-values occurring in practice and for three

[1] Submitted for publication, Febr. 15, 1946.

values of t, viz. 20° C (for measurements on wax phantoms etc., when the room temperature is approximately 20°), 32° C (for measurements on the patient's skin), and 37° C (for measurements inside body cavities like the mouth, throat, rectum, etc.).

Formerly, the calculations used to be done in the following manner. The correction factor, which is generally the same for several measurements

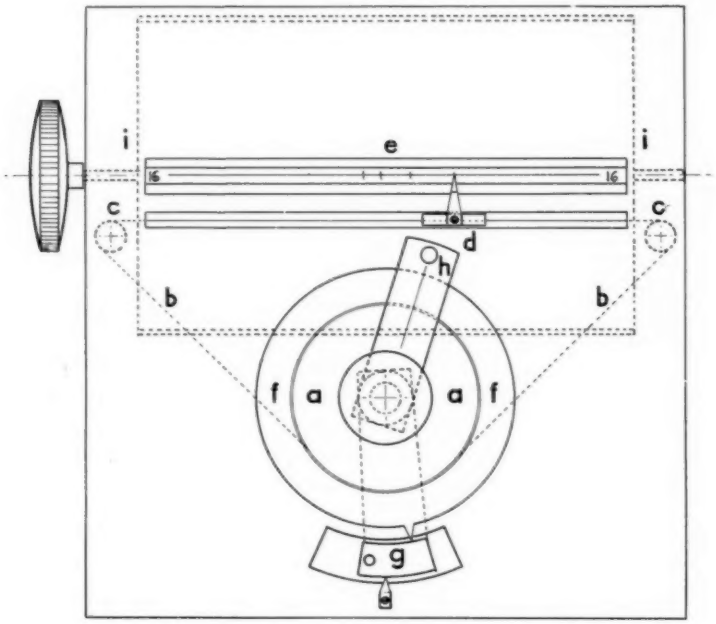

Fig. 1.

on the same day, is found in the table, and the loss of potential for each chamber is multiplied by it. This corrected value is multiplied by the constant k — found in another table — for each chamber and radiation quality used for the irradiation. The new instrument replaces all these operations by the few simple manipulations and scale readings described below.

The different factors are multiplied by aid of logarithmic scales, movable in relation to each other as in the ordinary slide rule but specially arranged for this particular problem.

The scale for loss of potential is engraved along the circumference of a circular disc a, which in the prototype has a diameter of 78 mm (circumference 245 mm). See the diagram Fig. 1—2. The scale covers an interval

of 1 : 10 (30—300 V). The accuracy is thus practically the same as in an ordinary 25 cm slide rule, an error of setting of 1 mm corresponding to an error of about 1 %. It is easy to set the scale to a fraction of a mm, which is amply sufficient, as other sources of error dominate in these measurements, giving an aggregate uncertainty which can usually be estimated at 4—5 %.

The disc is attached to an axle carrying also a wheel with a grooved rim; the diameter at the bottom of the groove is equal to that of the scale. A cord b is fixed to the wheel passing round it and over the pulleys c c, between which it is fixed the slide d. This carries a pointer moving along the logarithmic scale e, when the circular scale a, and with it the wheel, are turned by aid of a knob, to set the pointer to the value of the constant k for the chamber and ray quality in question. The angle v between the initial division of the scale (30 V) and a vertical plane through the axis of rotation is thus, except for an additive constant, proportional to log k. We have $v = 360 \log k + C$ if v is expressed in degrees. The voltage scale division corresponding to a certain loss of potential d lies in the angle $v_1 = v + 360 \log d/30 = 360 \log kd/30 + C$. The dose value D corresponding to d is read on a circular scale f outside the voltage scale and concentric with it. This scale runs from 60 to 600 r, making the angle between the initial division and the division of the dose D equal to 360 log $D/60$. If the dosage scale is turned through an angle corresponding to the negative logarithm of the correction factor $c = \frac{760}{b} \cdot \frac{273 + t}{293}$, it is easy to prove that — once the instrument is properly adjusted — the corresponding values of d and D will be exactly opposite each other. The latter value will be found at the angle $v_2 = 360 \log D/60c + C_2$, where C_2 is another additive constant. From (1) we find $\log D/c = \log kd$ whence $v_2 =$

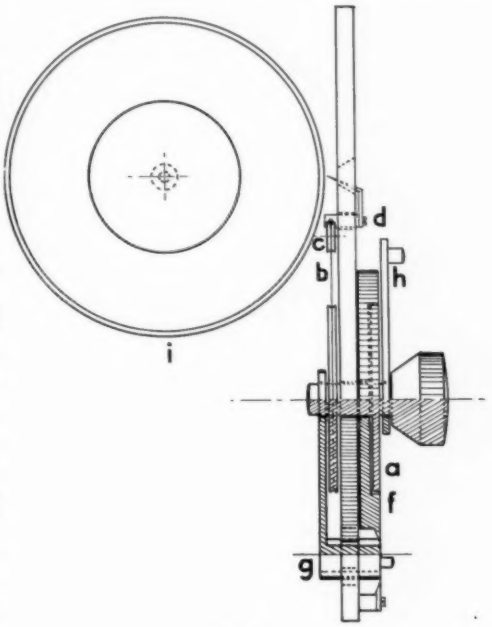

Fig. 2.

360 log $kd/60 + C_2$. If C_2 is made equal to 360 log $2 + C_1$, we get $v_1 = v_2$; in other words, the dose D corresponding to a certain loss of potential d will be read exactly opposite the division of d on the inner scale. The proper adjustment of the constants C_1 and C_2 to each other may be done in different ways: a) by turning the scale disc a and the corded wheel below it in relation to each other before fixing them to their common axle; b) by fixing different points of the string to the wheel or to the slide d; and finally c) by moving the scale e longitudinally.

The correction factor c is introduced by means of an arc g turning on the same axis as the circular scales. Its lower edge is graduated according to the function 360 log $760/b$ and its upper edge to 360 log $293/(273 + t)$. When the scale division of the arc corresponding to the barometric pressure is set opposite a fixed index, and the external circular scale f (dosage scale) is turned until its index points to the temperature of the chamber during the irradiation, the dosage scale must obviously have been turned through an angle which, but for an additive constant, equals $360 \log \frac{760}{b} \cdot \frac{273 + t}{293} = 360 \log c$. The said additive constant may be included in the constant C_2. After these settings (which are much more rapidly done than described) the dose can according to the above be read opposite the loss of voltage. This is facilitated by a transparent rule h on which a line is engraved.

In practice, no logarithmic scale is marked along the line e. This would necessitate the finding, for each calculation, of the chamber constant k from a table and then setting the pointer d to the corresponding division. To save this work, and to reduce the risk of error inherent in it, markings corresponding to the values of the different chamber constants are directly plotted along the line e, which thus forms a kind of graphical table.

Because of the large number of chambers (about 100) in use at the Institute for routine measurements, this scale would become quite illegible if all values were plotted along the same line. As each chamber is used with four different ray qualities, the scale would have about 400 very unevenly spaced and often overlapping markings. A separate scale carrying four marks for the standard qualities used at Radiumhemmet (100—105 kV, additional filter 1 mm Al; 140—145 kV, 4 mm Al; 165—170 kV, 0.5 mm Cu + 1 mm Al; and 165—170 kV, tin-filter according to THORÆUS) is therefore provided for each chamber. The standard qualities are designated by different-coloured marks, so that the above dates need not be written beside the marks on the scales. For some chambers, the constants of two different qualities happen to be exactly equal, in which case two oblique markings in the corresponding colours are drawn to intersect at the correct point on the base line of the scale.

Even if three or four constants should be equal, it is easy to mark them distinctly and separately on the same point of the scale.

Rapid setting of the scale of any chamber whose reading is to be calculated is essential. The scales are therefore drawn on paper wrapped round a cylinder i, 16 cm in diameter in the prototype. This gives a circumference of about 50 cm, or 5 mm to each scale. The cylinder is placed behind an oblong window in the front plate, which shows only one scale at a time. The number of the corresponding chamber is written at both ends. In practice, the lines and numbers are drawn on transparent paper from which photo-copies are taken. Each time the chambers are re-calibrated (usually once a year), a new copy is fixed to the cylinder and the constants are marked. The correct place of the markings is determined by the fact that eq. (1) for $d = 100$, $b = 760$, and $t = 20$, assumes the simple form $D = 100\ k$. If the pointers on the correction scales are set to 760 and 20, and the disc a is turned until the division for 100 V on the voltage scale is opposite the division for $100\ k$ on the dose scale, the pointer on the slide d will thus show where the marks are to be made.

SUMMARY

The present paper describes an instrument simplifying the calculation of roentgen doses from condenser chamber readings by the aid of suitably arranged logarithmic scales.

ZUSAMMENFASSUNG

Die hier vorliegende Arbeit beschreibt ein Instrument, das die Errechnung von Röntgendosen aus Kondensatorkammerablesungen mit Hilfe von entsprechend angeordneten logarithmischen Skalen erleichtert.

RÉSUMÉ

Le travail présenté décrit un instrument qui facilite le calcul des doses de Rayons Roentgen par la lecture d'une chambre condensateur en s'aidant d'échelles logarithmiques judicieusement disposées.

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THE MINERAL METABOLISM IN THE DENTAL HARD TISSUES[1]

Tracer experiments in vivo with ^{32}P and ^{24}Na

(Preliminary report)

by

Helge Berggren, Borås

Introduction

In recent papers I have given preliminary reports of certain investigations on the permeability of the dental hard tissues. As a medium of investigation methylene blue was used in the majority of the cases, and with this dye I obtained a distinct staining of limited enamel areas via the dentin. No penetration of the dye from the enamel surface was established.

The possibilities of studying the pathways of the dental hard tissues have increased considerably, since through the access of the radioactive isotopes of calcium and phosphorus we have got the opportunity to use these substances, normal constituents of enamel and dentin.

The use of labelled isotopes with which the metabolism of a single dose of ingested substance may be traced, offers a suitable method for studying the inorganic metabolism of the teeth. Since the radioactive isotope of calcium, the largest single mineral constituent of the teeth, has certain properties that make it difficult to work with, the more suitable radioactive isotopes ^{32}P and ^{24}Na were selected for this study.

History

The first to extend his experiments with the radioactive isotopes to comprise also the metabolism of the dental tissues was HEVESY.

[1] Submitted for publication, Jan. 12, 1946.

In 1935, CHIEWITZ and HEVESY employed ^{32}P in the first metabolism study utilizing an artificial radioactive isotope. Two years later, the same investigators added sodium radiophosphate to the diets of rats and discovered that an appreciable portion of the radioelement quickly found its way into the bones, teeth, muscles and other tissues of growing and adult animals.

HEVESY, HOLST and KROGH demonstrated a phosphorus turn over in incisors and molars of rats as well as in human and cat teeth. The phosphorus metabolism in teeth was observed to be considerably less than in bone. It was therefore the phosphorus metabolism in the calcified tissues as a whole that was investigated. No distinction between dentin and enamel or between the superficial and the deep enamel layers was made.

HEVESY and ARMSTRONG proved that only an inconsiderable amount — 0.005 % — of the injected dose of ^{32}P was found in the enamel. In the dentin about 10 times more.

MANLY, HODGE and van VOORHIS were not able to establish any phosphorus absorption in the enamel probably because the preparation of radiophosphorus injected was too weak to activate the enamel to a measurable degree.

VOLKER and SOGNNAES reported a phosphorus metabolism in the enamel and later that a great part of the phosphorus in the superficial enamel layer comes from the saliva. They also proved that about equal parts of ^{32}P are metabolized in the dentin and enamel of unerupted teeth. On the other hand the phosphorus metabolism in the enamel of erupted teeth is about 1/7 of that of dentin.

VASSERMAN and his collaborators examined pulpless teeth both with and without metal caps and proved that only insignificant quantities of ^{32}P in vivo from the saliva are absorbed by enamel and dentin.

From a cat which had been injected with ^{32}P, BARNUM and ARMSTRONG found, after five days, that the P. content in 1 gm enamel ash and 1 gm dentin ash was 0.000546 % and 0.00878 % respectively. For the sake of comparison the P. content in 1 gm femur diaphysis ash was 0.0133 %, in 1 gm femur epiphysis 0.0611 % and in 1 gm femur marrow 0.311 %.

CAMPBELL and GREENBERG used radioactive calcium for in vivo investigations of the calcium metabolism. They stated that the quantities of the radioactive isotope resorbed by equal parts of bone and whole teeth were roughly the same.

In recent years P. O. PEDERSEN and BODIL SCHMIDT-NIELSEN of Copenhagen have made experiments with peroral administration of ^{32}P on four persons 10—19 years of age. Further, in vitro experiments have been carried out with 15 newly extracted teeth immersed in tubes con-

taining radioactive saliva. The tubes were kept in incubator from 11 to 24 days. The authors established exchange of P-atoms between saliva and intact superficial enamel. The quantity is proved to be the same in vivo and in vitro. A measurable exchange between dentin and enamel could not be stated. The last mentioned observation was made during the in vivo experiments where the tooth crowns were isolated from the saliva by means of metal caps.

An etched enamel surface was observed to absorb ten times more than an unetched one in experiments in vivo as well as in vitro. The authors further say that the deep enamel layer was not investigated because the risk of contaminating the enamel samples with dentin was too great. Not even with the procedure of MANLY and HODGE can one be sure of getting samples absolutely free from dentin.

My own investigations

Experiments on animals.

My own investigations with ^{32}P and ^{24}Na have comprised experiments on animals as well as on human beings. For the registration of the β-particles the Geiger-Müller counter has usually been used, but experiments with photographic registration have also been carried out. Thanks to Professor SIEGBAHN about 12 mC ^{32}P and 30 mC ^{24}Na have been received for carrying out the investigations.

In the beginning the experiments aimed at getting a practical method and, by injection on dogs, of obtaining an idea about the influence of the β-particles on the leucocytes, as well as the general influence of the preparation on the condition of the animals. From the experiments on animals I have also secured a considerable number of teeth for the testing of suitable photographic material for the registration of the β-particles and for finding out the necessary time of exposure.

The counting of the leucocytes has given such varying results that experts do not consider that they ought to draw any conclusions from that. However, the injected quantities — maximum 2 mC — do not seem to be of a size making it dangerous to inject or ingest up to 1 mC in man. In U. S. A. activities many times as high have been used in experiments on human beings.

As, in this report, I only intend to describe the method used in the experiments, only a summary report on the results will be given. I intend to give a more detailed report on them later on.

For the experiments with photographic registration I collected the molars in order to prepare ground sections of the uniform thickness of 200—300 μ. To reduce the diffusion of the β-particles, emanating from a

thick preparation it is of course desirable that sections should be as thin as possible. However, this will cause a decrease in the activity, and in very thin sections the activity is so insignificant that no impression is produced on the photographic plate.

As negative material I first tried the Autolithe and Printon plates (Agfa) used in the chemigraphic industry, but they did not appear to be sufficiently sensitive for the weak radiation. Later on experiments were carried out with the K-plate (Agfa), specially intended for the registration of corpuscular radiation. Nor could satisfactory results be obtained with these plates, probably owing to bad quality during the war.

At the photographic laboratory of the Royal Technical University, Stockholm, in the spring of 1945 I had an opportunity of trying the spectral plates Blau Rapid (Agfa), and they appeared to be more suitable for the experiments. Ground sections of a thickness of 1/4 mm from molars of dogs were prepared after injection of about 1 mC ^{32}P given 4 hours before the animals were killed. The sections were placed on the photographic plates and heavy glass slabs were used as weights over the preparations. Time of exposure 3 weeks. Clear pictures were now obtained, but unfortunately it was impossible to see any details concerning the phosphorus absorption in the pictures. (Figures 1 and 2.) The border lines were too diffuse to permit the observation of any difference in the radiation from enamel and dentin if there was one. Besides the radiation had affected the plate even outside the border lines of the preparations, and I had to content myself with the observation that the β-radiation from these ground sections is of such an intensity that a photographic registration is possible. The same thing may be stated about the pictures published by EHRBACHER.

From the observatory at Saltsjöbaden I afterwards received a box of Eastman Spectroscopic Plates which came better up to requirements. With the same thickness of the sections I obtained well limited pictures, which probably may be subjects for studies in detail. (Figures 3 and 4). In this case the teeth sectioned for photographic registration came from a dog injected with about 20 mC radioactive sodium (^{24}Na, half life 14.8 hours). From this radioelement the β-radiation is followed by a harder γ-radiation, and it is not inconceivable that this hard γ-radiation contributed to the better result, as of course the large injected dose did. Time of exposure one week.

Certain teeth have also been collected from the experiment animals for measuring the enamel activity in the Geiger-Müller counter. The results from seven dogs are available, five of which received ^{32}P in doses varying from 0.6 to 1 mC, and two ^{24}Na, 10 respectively 20 mC.

In order to eliminate the influence of the saliva, three incisors in the maxilla of the first two dogs had been fitted with caps of Randolph

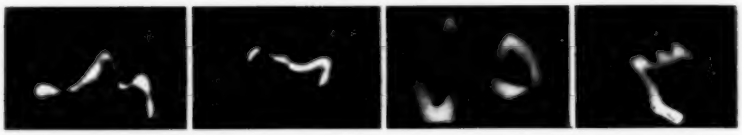

Fig. 1. Fig. 2. Fig. 3. Fig. 4.

metal or gold before being injected with 1 mC ^{32}P. Moreover on one of the dogs rubber dam was applied on the upper medial incisors which were extracted after only one hour.

On the remaining animals rubber dam was usually applied to all incisors in the maxilla. The animals were killed after 2½ to 4 hours and the teeth were extracted whilst great care was taken to prevent the crowns from being contaminated with radioactive saliva.

Certain authors have emphasized the difficulty or impossibility of obtaining samples entirely free from dentin with the processes hitherto known. Not even the procedure of MANLY and HODGE is regarded as reliable. For the measuring of the radioactivity of the enamel I have therefore used a method for its separation from the dentin which hitherto has not been applied to investigations of this kind. After a suggestion by Professor HEVESY — previously mentioned by PICKERILL — a method has been worked out to bring about this separation by heating the tooth in an electric oven up to 400 to 500° C. At this temperature the dentin cone becomes charred after 1 to 2 minutes, and with a suitable instrument the enamel can be detached in quite big pieces. With a fine diamond instrument a black-brown layer very likely belonging to the dentin, is removed, whereafter perfectly pure enamel will remain.

In the first two cases the pure enamel was dissolved in 6 n. HCl, and the solution was evaporated on a watch glass and reduced to powder. The activity was then measured.

The pulverization was made between two eternite discs, new for every sample, in order to avoid transferring the activity to the next sample.

In certain cases the enamel fragments from molars exposed to the saliva obtained after heating were embedded in litharge mixed with glycerine. The enamel layer facing the dentin was free, and from this layer the dark organic covering was removed by means of diamond instruments. Little by little the deep enamel layer was then ground away and collected for the measuring of its activity. Great care was taken not to penetrate the enamel at any point, by which the phosphorus without doubt adhering to the enamel surface would have »infected» the sample.

A comparison between the enamel activity in capped and uncapped

teeth shows that distinct activity was found even in the capped ones, where the influence of the saliva had been eliminated, but that it reached only 10 to 12 % of the enamel activity in uncapped teeth. The experiment is of interest, not only because it is the first time that measuring has been carried out on the total enamel quantity of the tooth which can be proved not to contain the least trace of dentin, but also because activity has been established for the first time in enamel not influenced by saliva.

The same interest is attracted by the experiments with rubber dam. Here, too, distinct activity was established on measuring the pulverized enamel in spite of the fact that the time of action of the radioactive preparation did not exceed a few hours. The activity varied between 1.19 ± 0.10 and 7.31 ± 1.06 counts per minute and per 100 mg of enamel substance, partly owing to variations in the quantity of injected activity (0.6—1 mC), partly to variations in the weight of the animals. All values are corrected to the day when the radioactive preparation was produced (0—day) and indicated per 100 mg of enamel substance.

The enamel from the teeth with rubber dam of the dogs injected with ^{24}Na also proved to be distinctly radioactive. Here too the activity varied with regard to injected amount (10 and 20 mC respectively) and the weight of the animals (14 and 26.8 kg. respectively). For the sake of comparison I also measured the activity of the deep enamel layer obtained by grinding from within the enamel of molars influenced by the saliva. Practically identical values were obtained.

The results of the experiments with sodium are of special interest, since this substance forms part of the enamel only to an inconsiderable extent. On the other hand it is found in the intercellular fluid, for which reason its presence in the enamel must indicate a fluid current in this tissue.

Experiments on man.

In doses varying from 1/4 to 1 mC, ^{32}P has been administered per os to 19 persons and intravenously to one. In this way 38, as far as I have been able to find out, intact teeth have been obtained for the determination of enamel activity.

In these cases, too, gold crowns (5) and rubber dam (9) have been applied on certain teeth.

The phosphorus distribution in the enamel of teeth fitted with crowns was always, in the human as well as in the animal material, compared with the distribution in the corresponding teeth not fitted with crowns in the same individual.

In all cases radioactivity has been found in the enamel of the crowned teeth but, as was the case with the dog teeth, the values have been from

10 to 50 % less than the corresponding ones of the teeth influenced by the saliva.

On a boy, 12 years of age, two bicuspides on which rubber dam had been applied, were extracted 3 hours after administration of 0.8 mC ^{32}P. As a further precautionary measure against any trickling of saliva, copper shells were fastened by means of a cervical strip of oxyphosphate cement. In order to keep the teeth moist the shells were filled with inactive saliva. In these two as well as in six of the remaining seven teeth fitted with rubber dam and extracted only a few hours after the ingestion or injection of the radioactive preparation, distinct activity was found in the superficial enamel layer. Activity was also found in the ninth tooth, but the value was not statistically sure — 1.02 ± 0.52 counts per minute. In all the teeth there was distinct activity in the deep layer obtained by the previously mentioned method. It should be observed that the intravenous injection of 1 mC ^{32}P was made on a woman 43 years old at Radiumhemmet. Even at this relatively great age a phosphorus metabolism via the pulp and dentin into the enamel was established.

On 17 persons 24 teeth were not extracted until 2—30 days after administration of 1/4—1 mC ^{32}P. In 25 % of these teeth from 4 persons, activity was not established or the values were not statistically secure. On the other hand in 75 % unmistakable activity was found in both superficial and deep layers.

This fact must prove a phosphorus distribution in the enamel via pulp and dentin which is also proved by the investigations on animals.

The phosphorus content in the crown dentin has proved to be from 7 to 10 times larger than in the enamel and about half as large as in the root dentin. In the experiments on animals greater differences have been observed, and the content in the dentin in these cases has been up to 50 times larger than in the enamel.

The fact that a distribution in the enamel is brought about via pulp and dentin does not, however, necessarily exclude a turn over from the saliva also via the superficial layer of the enamel. In order to investigate this possibility, experiments were carried out to supply the phosphorus only from without. On 8 teeth — upper bicuspides — rubber dam was applied. On the crown of each tooth cotton, saturated with Na_2HPO_4 containing ^{32}P, was placed. The teeth were extracted after 2—4 hours without removing the dam. While the tooth was still kept in the forceps the apical half of the root was cut away with a thin diamond disc. This part of the root was heated and then pulverized, and the activity was measured. The rubber dam was removed from the tooth crown, which was then heated in an electric oven. In these cases the teeth were kept in the oven, until the enamel was detached by explosive force

from the dentin cone. After pulverizing, the activity of the crown dentin was also measured. That phosphorus penetrate into the enamel from this side, too, is beyond doubt, as distinct activity was established in both root and crown dentin. The content in crown dentin was about twice as large as in root dentin.

Part of these investigations have been made possible by scholarships from the Caries Fund of Dentalaktiebolaget, for which I beg to express my sincere acknowledgement.

I am also much obliged to Professor M. SIEGBAHN for his great kindness in giving me radioactive preparations, to Professor G. HEVESY and Professor G. WESTIN for the interest they have shown in the planning of my investigations, to Professor J. RUNNSTRÖM, Professor A. HJÄRRE and Docent H. BÄCKSTRÖM for their great obligingness in giving me the opportunity of working at their respective institutes.

Docent L. GOLDBERG has checked the results of the investigations from a statistical point of view, and in doing so he has given me much valuable advice, for which I also beg to thank him here.

In the course of the investigation I have also been given valuable assistance by Fil. Lic. MIGNON MALM, Wenner-Gren's Institute, Fil. Mag. H. ATTERLING, Research Institute for Physics, Fil. Mag. A. BOSTRÖM, Photographic Laboratory of the Royal Technical University, Laborator HEDSTRÖM, Konsulent SANDSTEDT, Assistent SWAHN, State Veterinary Medical Institute and Stadsveterinär TULLBERG, Borås, all of whom I heartily thank for their valuable help.

SUMMARY

The author accounts for investigations with the radioactive isotopes ^{32}P and ^{24}Na as tracers to show the permeability of the dental hard tissues. A description of the methodes is given. Experiments were made with dogs and humans, who got the preparations intravenously or perorally. Rubber dam and metal caps were applied on certain teeth.

Samples for the measuring of the enamel activity were produced with a new method. Activity was stated in all teeth isolated from the saliva by means of caps or rubber dam also in the deep enamel layer of the majority of the teeth influenced by the saliva. Photographic registration of the β-radiation from ground sections from 200—300 μ of molars of dogs injected with 1 mC ^{32}P and with 20 mC ^{24}Na has been carried out. Phosphorus turn over from the enamel surface was stated in 8 cases where radioactive P-solution was placed outside the teeth after rubber dam application. Distinct radioactivity in the root dentin.

ZUSAMMENFASSUNG

Der Verfasser berichtet über gewisse Untersuchungen mit Hilfe der radioaktiven Isotopen ^{32}P und ^{24}Na über die Durchlässigkeit der harten Zahngewebe und beschreibt die angewandten Methoden. Die Untersuchungen haben sowohl Tier- als Menschenversuche umfasst, und die Präparate sind intravenös oder peroral gegeben worden. Kofferdam und Metallkronen sind auf gewissen Zähnen angebracht worden.

Schliffpreparate für die Messung der Aktivität des Schmelzes sind nach einer neuen Methode hergestellt worden. Aktivität ist in sämtlichen Zähnen festgestellt worden, die durch Kronen oder Kofferdam von dem Speichel isoliert waren, wie auch in der tiefen

Schmelzschicht in 75 % von allen Zähnen, die unter dem Einflusse des Speichels gestanden hatten. Photographische Registrierung der β-Strahlung von Schliffschnitten 200—300 μ von Hundemolaren ist nach Injektion von 1 mC ^{32}P und 20 mC ^{24}Na gemacht worden. Phosphoreinwanderung von der Schmelzoberfläche aus ist in 8 Fällen konstatiert worden, wo radioaktive Phosphorlösung auf der Aussenseite der Zähne unter Kofferdam appliziert worden war. Deutliche Aktivität im Wurzeldentin.

RÉSUMÉ

L'auteur rend compte de certaines investigations de la perméabilité des tissus durs des dents avec l'aide des isotopes radioactives ^{32}P et ^{24}Na et décrit les méthodes employées. Les investigations ont compris des expériences d'animaux et d'hommes, et les préparations ont été données par injection ou par ingestion. Du cofferdam ou des couronnes en métal ont été appliqués sur certaines dents.

Les préparations pour mesurer l'activité de l'émail ont été produits par un nouveau procédé. De l'activité a été constatée dans toutes les dents isolées de la salive par des couronnes ou du cofferdam ainsi que dans la couche profonde de l'émail dans 75 % des dents influencées par la salive. L'enregistrement photographique de la β-radiation a été exécuté au moyen de tranches très minces, 200—300 μ, des dents molaires de chiens après l'injection de 1 mC ^{32}P et de 20 mC ^{24}Na. La pénétration du phosphore de la surface de l'émail a été constatée dans 8 cas où une solution de phosphore radioactif a été appliquée sur les dents sous du cofferdam. Activité visible dans la dentine des racines.

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FROM THE ROENTGEN-DIAGNOSTIC DEPARTMENT OF THE CAROLINE HOSPITAL, STOCKHOLM
(CHIEF: PROFESSOR Å. ÅKERLUND)

ON RETROCARDIAC PULMO-PLEURAL DEMARCATION LINES AND THEIR DIAGNOSTIC SIGNIFICANCE[1]

by

L. Billing

As pointed out by N. EDLING (1) of the Roentgen-Diagnostic Department of the Caroline Hospital, the contours of the pulmo-pleural demarcation lines should always be specially observed in radiographs of the lungs, as any defects in or absence of such contours is a sign of some pulmonar or pleural pathological process. A pleural process will as a rule displace or delete a considerable portion of the lung contour. As mainly minor local breaks in the contour will be discussed here, I shall in the following speak only of parenchymatous indurations. Our continued experience in the Roentgen Department has also proved that this indirect sign of a parenchymatous induration is particularly valuable in diagnosing retrocardiac processes, as a defect in the normal aorta contour (A in Fig. 1) is fairly often the only unequivocal sign of some slight lung process which cannot be projected free, whatever the direction of the beam. Such defects in the contour are not always of any pathological significance, however, as they may also be due to some anatomical variation in the posterior mediastinum. In order to demonstrate this, and to make clear why this indirect sign is so very useful, an account will be given below of the physical and anatomical basis of this diagnostic.

The physical conditions are less favourable for the observation in the Roentgen picture of pathological processes in those parts of the lungs which no beam direction will project free of the vertebral column, the mediastinum, the heart or the diaphragm (the area marked in Fig. 2) than when the processes occur in other parts of the lungs.

A roentgen picture is a photographic record of differences in absorption of the radiation. The absorption of a beam that has passed through non-aeriferous lung tissue will differ less from that of an adjacent beam that

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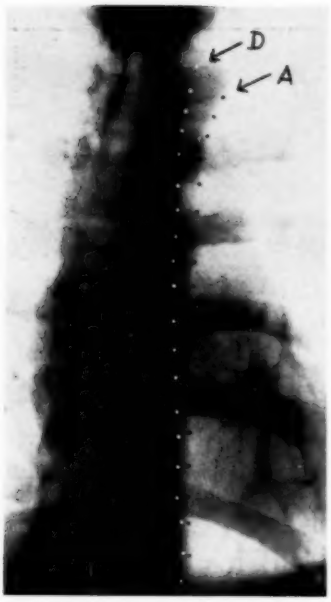

Fig. 1. Penetrating exposure with almost sagittal beam direction. A is the pulmo-pleural demarcation line at the aorta (the aorta contour). D is the border line between the paravertebral soft parts and the lung.

has passed through normal lung tissue if the surrounding soft layers are thick than if they are thin. The reason for this is that the absorption curve is exponential, and the effect of this, which is a diagnostic drawback, is increased by the scattered radiation. In photographing details of the retrocardiac parts of the lungs, the differences in absorption will be relatively small. It is important that these should be recorded in the steepest part of the density curve of the film.

An opinion of these parts of the lungs can only be obtained from pictures taken with considerably heavier exposure than the usual frontal pictures (sagittal radiation), and with the use of a grid. »Penetrating exposure» accordingly seems to me a better designation of this technique than »over-exposure» (STEIN) or »well-exposed picture» (EDLING)

Radiographically, the visibility of the pulmo-pleural demarcation lines in the roentgen pictures is contingent on a beam's touching tangentially for a minimum distance of 3—4 mm a surface separating aeriferous lung tissue from the pleura and the soft parts adjoining this, as do for instance A and B in Fig. 3. The longer this distance, the more distinct will be the pulmo-pleural demarcation line in the picture. If the beam is only tangential to a sharp edge of the lung, no such contour will appear in the picture. The lower edge of the lung is therefore not normally visible in the radiograph. If the pulmonary parenchyma adjoining a broadly touched separating surface is not aeriferous, there is nothing to produce the contour line, and a defect in or absence of a pulmo-pleural demarcation line is accordingly an indirect sign of some pathological process.

Under certain circumstances a pulmonary process is easier to observe by this indirect sign than directly as an density. A dense area in the roentgen picture catches the eye more easily if it is homogeneous, regular, and sharply defined against its surroundings, than if the opposite. For that reason the pulmo-pleural demarcation lines are relatively easy to see. This also applies to retrocardiac pulmo-pleural demarcation lines, although

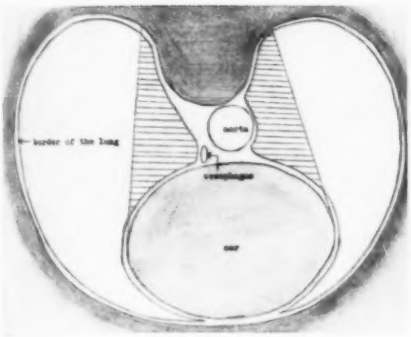

Fig. 2.

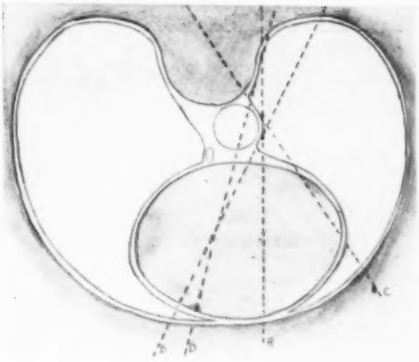

Fig 3.

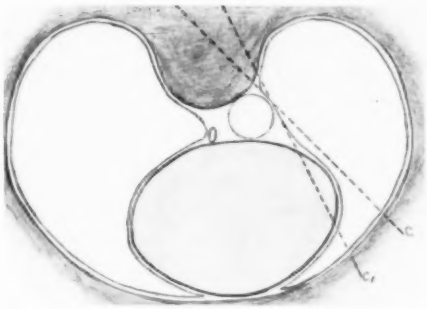

Fig. 4.

Fig. 2. Schematic cross section of the thorax below the lung hilus. The shaded area indicates those parts of the lungs which cannot be projected free of heart, spine, and mediastinum, whatever the direction of the beam.

Fig. 3. Schematic cross section below the lung hilus of a normal thorax with great heart to spine distance. The sagittal beam A is tangential to the surface separating the aorta from the lung, and produces the aorta contour. B and C show how far the beam may deviate from the absolutely sagittal direction and yet remain tangential to that border surface.

Fig. 4. Like Fig. 3, but a case of short heart to spine distance. As long as the direction of the beam is between C and C_1, but not absolutely sagittal, it is tangential to the aorta—lung border surface.

in their case the differences in absorption are small owing to the beam's passing only a relatively narrow tangential surface and penetrating strongly radiation-absorbing tissues anterior and posterior to it. This explains why it is often easier to see a defect in a sharp contour line than a small, diffuse induration causing that defect.

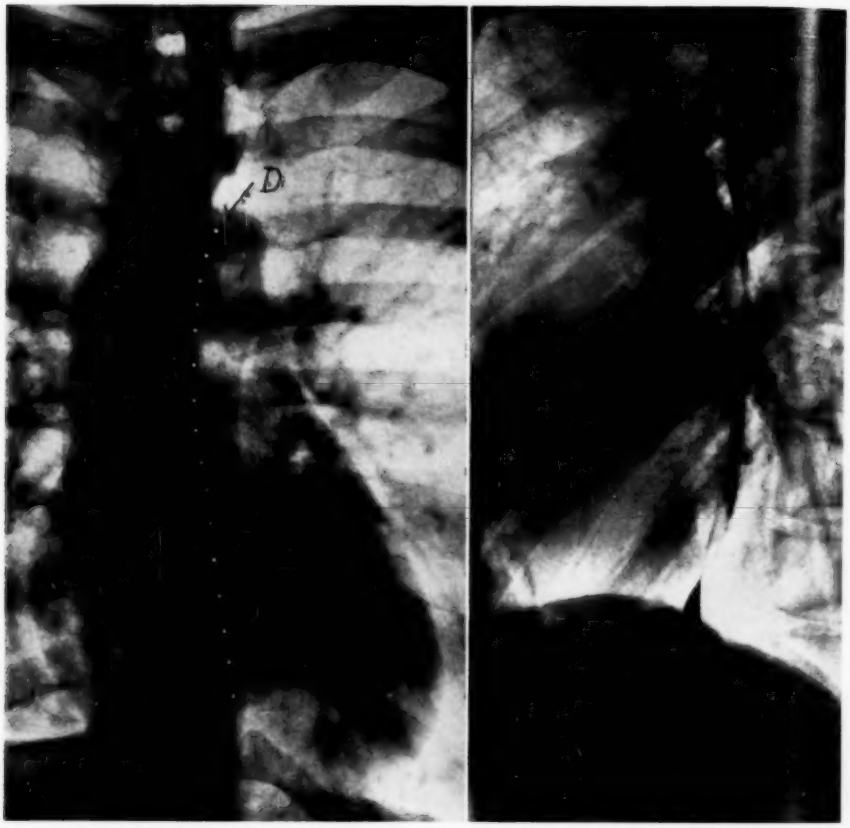

Fig. 5 a. Fig. 5 b.

Fig. 5 a. Penetrating exposure with sagittal beam direction in a case of short heart to spine distance. The aorta contour shows an »anatomical» defect A_1. The paravertebral pulmo-pleural contour D is unbroken.

Fig. 5 b. Lateral view of the same case, demonstrating the short heart to spine distance.

A proper appreciation of this indirect sign presumes a knowledge of the course of normal pulmo-pleural demarcation lines. The lines which in practice are most useful to observe are: the border line between the diaphragm and the lung in both frontal and lateral view, the retrocardiac pulmo-pleural demarcation lines in frontal view, and the border line between the posterior wall of the thorax and the lung in lateral view. Here,

however, we will only mention the retrocardiac pulmo-pleural demarcation lines on the left side.

The appearance of the aorta contour (A in Fig. 1), which depends on the incidence in the lung of the aortic sulcus, is shown in Fig. 3, which is a schematic cross section of the thorax some 4 cm below the lung hilus. This sketch is based on a number of radiographs of a normal case taken in different directions. In the direction A the beam is tangential to the border between the aorta and the adjoining part of the lung. B and C indicate how much the beam may be deflected from the sagittal plane before this border line disappears from the Roentgen picture. D in Fig. 3 shows correspondingly how to produce the demarcation line between the paravertebral soft parts and the left lung. This pulmo-pleural demarcation line (D in Fig. 1) is as a rule more distinct when the beam is slightly oblique as D in Fig. 3 than when it is absolutely sagittal, and demands a very penetrating exposure.

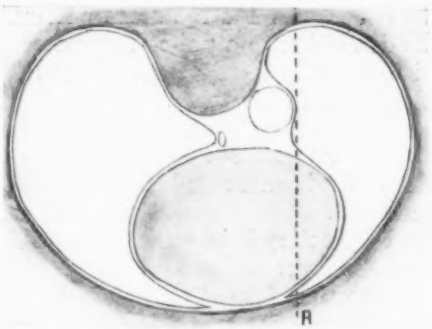

Fig. 6. Like Fig. 3, but a case of short heart to spine distance. The aorta is displaced to the left and posteriorly. Sagittal radiation will be tangential to the border surface between the aorta and the lung.

In cases where the posterior border of the heart is nearer to the vertebral column, the lung border takes a different course at the posterior mediastinum. Fig. 4 shows such a case drawn in the same way as Fig. 3. Only if its direction is between C and C_1 will the beam then be tangential to the border line between the aorta and the lung. If the beam is absolutely sagittal, on the other hand, no aorta contour will be visible. The least distance from the heart to the aorta is as a rule approximately midway between the lung hilus and the diaphragm, and that is where an anatomically conditioned local defect in the aorta contour may most frequently be observed in frontal pictures taken with penetrating exposure (A_1, Fig. 5). This happens in about 1 or 2 % of the adult cases, but apparently much more commonly in children. More rarely there may be no aorta contour at all below the lung hilus. In the 15 cases of anatomical defects in the aorta contour of this kind observed by the author, the distance between the posterior border of the heart and the spine at the defect was never more than 2 cm, or $^2/_3$ of the sagittal width of the vertebral body. The posterior border of the heart was in these cases assumed to be immediately anterior to the contrast-filled esophagus.

If the aorta contour is unbroken in one examination, and is found to

be defective when the same patient is examined later, this change may be due either to a pulmonary process, or — if the heart has increased in size sagittally — to a change in the direction of the border surface between the lung and the aorta.

But the aorta contour may often be quite distinct in the frontal picture even if the heart to spine distance is very short. In such cases the aorta is more or less displaced to the left and posteriorly, as shown in Fig. 6.

In practice it is generally possible to decide whether a defect in the aorta contour is due to a pathological pulmonal or pleural process or to the abovementioned anatomical conditions. Generally it is sufficient to estimate the heart to spine distance in the lateral picture. In other cases oblique pictures with the beam directed as C—C_1 in Fig. 4 may give a clear aorta contour. The demarcation line towards the paravertebral soft parts is an additional guide. If both these contour lines are defective at the same level, a pathological process extending backwards to the spine may be indicated. If the aorta contour alone is defective, this may be due either to merely a small process close to the aorta, or else to the anatomical condition mentioned above. Besides these indirect signs, a retrocardiac lung process may of course often be directly observed as a density.

SUMMARY

The author stresses the importance pointed out by N. Edling of observing the contours of the pulmo-pleural demarcation lines in a thorax radiograph, as a defect in that contour is an indirect sign of a pathological pulmonal or pleural process. The author describes the physical and anatomical basis of this diagnostic method, and shows that variations in the anatomy of the posterior mediastinum may be the cause of a defective aorta contour, which — if that possibility is not taken into account — may result in a wrong diagnosis.

ZUSAMMENFASSUNG

Verf. betont die Wichtigkeit dessen, dass man, wie N. Edling angegeben hat, im Thoraxradiogramm die Konturen der Lungen-Pleuragrenzen beobachtet, da eine Unterbrechung solch einer Kontur ein indirektes Anzeichen eines pathologischen Vorgangs in der Lunge oder Pleura darstellt. Verf. berichtet über die physikalische und anatomische Unterlage dieser Diagnostik und weist nach, dass eine anatomische Variation des hinteren Mediastinum eine Unterbrechung der Aortenkontur verursachen und, bei Nichtberücksichtigung dieser Möglichkeit, zu einer Fehldiagnose führen kann.

RÉSUMÉ

L'auteur souligne, ainsi que N. Edling l'a déjà relevé, combien il est important de préciser les contours des limites entre poumon et plèvre sur les radiographies du thorax, vu qu'une solution de continuité d'un contour est le signe indirect d'un processus patho-

logique du poumon ou de la plèvre. Il expose quel est le substratum physique et anatomique de ce diagnostic et montre qu'une variation anatomique du médiastin postérieur peut créer une solution de continuite dans le contour de l'aorte et donner lieu à une erreur de diagnosticsi l'on ne tient pas compte de cette possibilité.

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FROM THE RESEARCH INSTITUTE FOR PHYSICS (HEAD: PROF. MANNE SIEGBAHN) AND THE RADIOPHYSICAL INSTITUTE (HEAD: PROF. R. SIEVERT)

RADIATION MEASUREMENTS ON A CONTINUOUSLY EVACUATED ROENTGEN TUBE FOR 400 kV[1]

by

Sigvard Eklund and *Sven Benner*

At the Research Institute for Physics a high-voltage accelerating tube has been built which is connected to a cascade generator for max. 400 kV (1). For the present the tube has only been used as a roentgen tube. A schematic drawing of the whole tube, excluding the anode, is given in Fig. 1. Uppermost is seen the high-voltage cap A, which has a potential of max. 400 kV. At the top are holes through which, by means of cords from a control cabin, it is possible to regulate different auxiliary voltages, which are necessary to focus the electrons from an electron source within the cap to a regular beam proceeding downwards in the tube. To the right in the upper part of the figure a bakelite shaft is seen which drives an A. C. generator inside the cap.

The electrode A is connected to the 400 kV terminal of the cascade generator through a damping resistance of 1 MΩ, and the electrode B is connected to the 200 kV terminal by means of a resistance of 500 MΩ.

The positions of the accelerating and focusing electrodes inside the insulators are shown by the dotted lines.

On the earth side an evacuation tube C is arranged. This is connected, through a valve D, to a molecular pump of the large type (2), pumping 60 l/sec. (3). The number of solderings in the tube including the target arrangement is about 50 and the number of rubber gaskets about 20. The vacuum is nevertheless very reliable.

The concentration of the beam may be controlled in the glass cylinders E and F by turning forward quartz plates. G is a magnetic lens, formerly used in an electron-microscope of SIEGBAHN's construction, and mounted here in order to obtain a more or less concentrated focus on the anode, without adjusting the auxiliary voltages in the top cap.

[1] Submitted for publication, March 6, 1946.

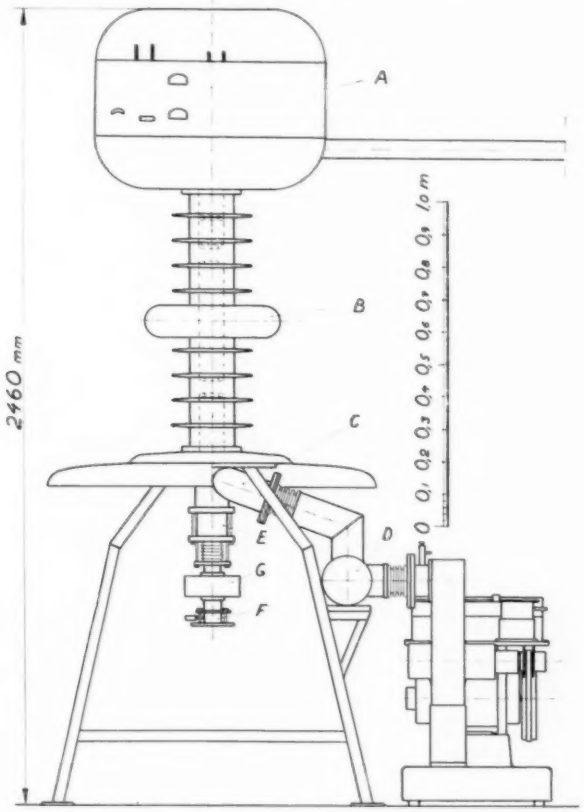

Fig. 1. The accelération tube with the molecular pump in the lower right-hand corner.

The target arrangement is shown in Fig. 2 a and b, which represent two different targets that have been used. The tungsten plate of Fig. 2 a and the tungsten cup of Fig. 2 b are provided on their outer surfaces with a layer of vacuum-fused copper. This permits good thermal contact to be attained by soldering to the surrounding brass.

When using the anode 2 a it is observed that a large part (c. 50 %) of the incident electron beam is reflected back and thus cannot be utilized for the production of roentgen rays in the tungsten plate.

On the basis of this experience the anode in Fig. 2 b was constructed. The target consists of a cylindrical cup of tungsten. Cooling water is forced through a spiral surrounding the vessel.

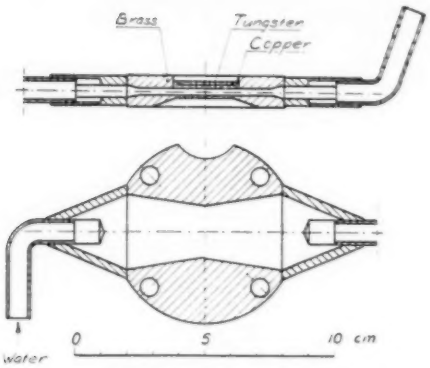

Fig. 2 a. Disc-shaped anode of tungsten.

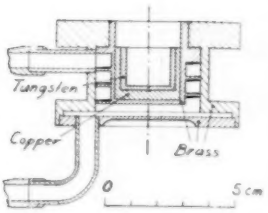

Fig. 2 b. Cup-shaped anode of tungsten.

The radiation from the anode 2 a is filtered through 2.0 mm tungsten, 2.3 mm copper, 1.3 mm brass and 3.0 mm water. The corresponding figures for the anode 2 b are 4.3 mm tungsten, 0.5 mm copper, 2.8 mm brass and 2.3 mm water.

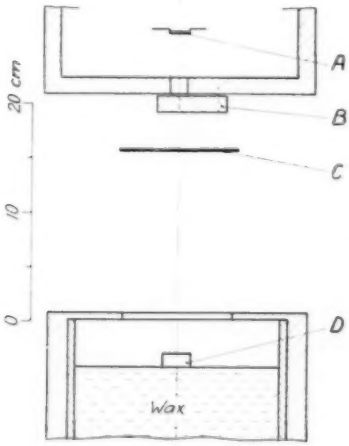

Fig. 3. *A* anode. *B* lead shutter. *C* copper absorber. *D* condenser chamber.

When the anode has a potential of + 200 V in relation to the surroundings, *i. e.* when the real secondary electrons released by the electron bombardment of the anode are stopped, 47 % of the incoming electron beam is reflected back at the anode 2 a and 19 % when using the anode 2 b.

All values of the radiation intensity in this paper refer to that part of the electron-current which is really absorbed in the anode.

The half-value layers and most of the dosage rate values were found with the arrangement shown in Fig. 3. The dosage rates include backscatter from a wax-phantom of which a surface 8.5 cm in diameter (57 cm²) was irradiated. The measuring instrument was a condenser chamber according to THORÆUS (4), to which an amber-insulated condenser was connected in order to reduce the sensitivity in the measurement of high dosage rates. A few dosage rate values were also taken in free air at 10 cm focal distance

with a large air condenser, protected from irradiation by a heavy lead screen, connected to the chamber.

For half-value layer measurements, copper layers of different thicknesses were inserted at C (Fig. 3). The dosage rates were expressed as percentages of the »zero values» with no copper layer inserted. One or two zero values were generally taken before and after each group of two to three measurements with copper absorber, and the latter were expressed as percentages of the average of the zero values before and after the group.

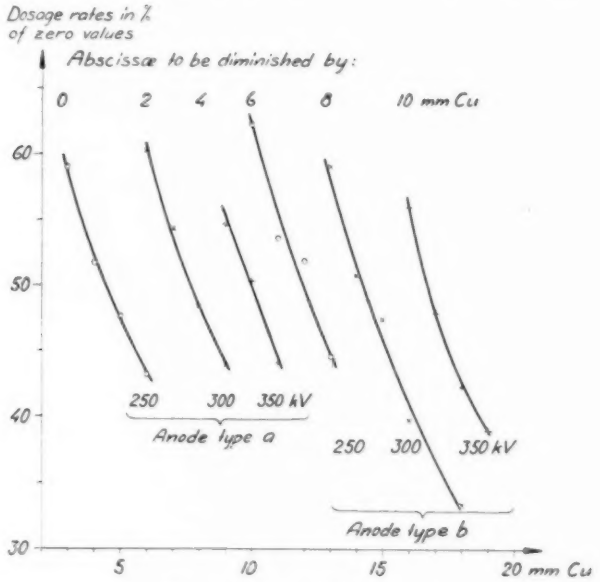

Fig. 4. Absorption curves.

The results are plotted in Fig. 4, where most points represent averages of several measurements. The half-value layers are found by graphical interpolation. In order to separate the curves better from each other, and thus to facilitate the reading of the graph, the origin for each curve has been displaced to the right through a distance corresponding to 2 mm. Cu with respect to the preceding curve. The abscissae for the different curves, except for the first, should therefore be diminished by 2 mm, 4 mm etc. These figures are written above the curves in Fig. 4.

The anode current in the roentgen tube was not the same in all measurements. To make the dosage rate values comparable, they were all divided by the anode current to give the dosage rate per mA. They apply to 29 cm

Table 1.

kV	Anode Fig. 2 a		Anode Fig. 2 b	
	r/min. per mA	Half-value layer (mm Cu)	r/min. per mA	Half-value layer (mm Cu)
250	1.0	4.4	0.05	6.0
300	4.1	5.6	0.40	6.2
350	11.2	6.0	1.60	6.6

distance and, as mentioned above, include back-scatter from an irradiated wax-phantom area of 57 cm². The values are given in Table 1 together with the corresponding half-value layers.

The dosage rate in air at 10 cm distance was only measured with anode 2 a and was found to be 100 r/min. at 350 kV and 140 r/min. at 378 kV. Because of the thinness of the chamber wall, these values may be somewhat too high owing to secondary electrons from the lead diaphragm below the anode.

SUMMARY

Measurements of dosage rates and half-value layers of the roentgen rays from a continuously evacuated roentgen tube are reported for voltages of 250—350 kV and for two different target designs.

ZUSAMMENFASSUNG

Die hier vorliegende Arbeit bringt Messungen der Strahlungsintensität und der Halbwertschicht bei Röntgenstrahlung aus einer kontinuierlich evakuierten Röntgenröhre bei einer Röhrenspannung von 250—350 kV und zwei verschiedenen Anodenkonstruktionen.

RÉSUMÉ

Les auteurs rendent compte de mesures de l'intensité, et des couches de demi-absorption des rayons émanant d'une ampoule Rœntgen à évacuation continue, pour des voltages de 250—350 kV et deux modèles differents d'anticathode.

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FROM THE INSTITUTE FOR RESEARCH IN ORGANIC CHEMISTRY, UNIVERSITY OF STOCKHOLM

INFLUENCE OF ROENTGEN RAYS ON ISOLATED CELL NUCLEI[1]

by

Hans von Euler and *L. Hahn*

With 4 Figures in the text

Many authors have discussed in what part of the cell the primary effect of roentgen rays takes place (1, 2). There may be several actions on different cell components in the cytoplasm and in the nucleus: at all events the action of roentgen rays is visible in the nucleus almost immediately after the commencement of the irradiation. Cells that would normally have entered mitosis, are inhibited at the beginning of the prophase; only cells in mitosis continue to divide (3). A short time after irradiation »primary action» of division is inhibited.

The sensitivity of cells to roentgen rays depends on their mitotic state (but also on several physical and chemical factors). The question as to the phase of the mitotic cycle in which the maximum of sensitivity to roentgen rays is reached, has been answered by many authors (MOTTRAM, SCOTT and RUSS (4), MARSHAK (5), SPARROW (6), NEWCOMBE (7) and VILLARS (7 b)) in quite different fashions. STRANGEWAYS & HOPWOOD (8) and JÜNGLING & LANGENDORFF (9) for example, found the maximum of sensitivity in the resting stage of the nuclei. Sensitivity maxima in two stages are referred to by HOLTHUSEN (10).

In tissue cultures the roentgen irradiation influences the mitotic rhythm to an extent depending on the period and dose of the radiation (11, 12, 13, 14). Small doses accelerate, high doses retard the process.

The influence of roentgen rays on *isolated chemically pure low-molecular substances* is generally very small. This is true *even of proteins*, and derivatives of nucleic acid, which are not split by roentgen rays except in very large doses.

[1] Submitted for publication, Febr. 11, 1946.

To what degree *enzymes* are sensitive to the action of ionising radiation is a more complicated question. Investigations by W. M. DALE (15, 16) and by A. FORSSBERG (17) on the stability of enzymes have shown the great influence of the medium (pH) on the radio-sensitivity, especially in the case of catalase.

EULER and HEVESY (18) isolated catalase from irradiated and non-irradiated rat Jensen sarcoma and from irradiated and non-irradiated muscle of normal rats. The activity of the enzymes studied (catalase and nuclease) *increased* after an irradiation with 3,000 r. The catalase reaction constant was

	before irradiation	after	Increase of k
k =	0.0252	0.0385	53 %

In FORSSBERG's experiments (l. c. pp. 3—4) on irradiation in vivo the activating effect of the irradiation on catalase, measured at pH 6.8, was somewhat lower.

The nuclease activity, measured by the amount of thymonucleic acid split in 4 hours, was (18)

before irradiation	after
46 %	66 %.

The values obtained in other experiments for the decrease of enzymic activities after irradiation are in many cases the resultants of the activating and the inactivating effects of the roentgen rays. The mechanisms of the two effects are probably very different.

The activating effect on enzymic activity is not specific for roentgen rays; it corresponds to the analogous effects of ultraviolet radiation and of heating to temperatures of 45°—60°, as observed by EULER & BLIX (19) and EULER & OHLSÉN (20).

W. M. DALE arrived at the conception of an intermediate radiation product, thus explaining the phenomenon of »protection» by other solutes present, which is difficult to understand on the basis of a direct action.

It is here not the place to discuss the »hit-theory» or the question whether the influence of roentgen radiation on organs and organisms is direct or indirect. In this respect we may draw the attention to R. SIEVERT's (21) theory for the effect of biological radiations, and to the research work and the discussion by A. FORSSBERG (22).

Experiments carried out in this institute (23) and the more extended investigation by A. FORSSBERG on the radio-sensitivity of catalase *in vivo* support the view that the enzymes are extremely radio-resistant in vivo, in contrast to the sensitivity of purified enzymes in aqueous solution.

In connection with the results obtained for the influence of roentgen rays on the nucleic acid metabolism in cancerous and normal tissues (12, 18, 24), it was of interest to establish whether roentgen rays were able to produce changes in cell nuclei isolated in such a state that their responses to roentgen rays would more or less correspond to the behaviour of irradiated cell nuclei in a living material.

DURYEE (l. c.) working with germinal vesicles from ovarian eggs of three species of frogs, was unable to confirm any radio-sensitivity of isolated cell nuclei; he used eggs both in the intact state and after isolation. His irradiation doses (8,000 r/min.) were graded from 500 to 50,000 r. When the cell nuclei were isolated subsequent to previous irradiations *in situ*, the chromosomes showed progressive injuries, starting from a dose of 1,000 r. But if the nuclei were first isolated and then irradiated, they showed, even after treatment with 50,000 r, no marked differences from non-irradiated controls. DURYEE emphasized, however, »the caution we must use in applying any of this information to other types of nuclei». He seems not to have obtained such nuclei quantities that would have enabled him to isolate their components.

If in DURYEE's experiments no radio-sensitivity of isolated cell nuclei could be detected, his negative results do not exclude that cell nuclei from other material, in a less damaged state, prepared and treated under other conditions, might give another response to irradiation than did the nuclei studied by this author.

It was of interest to examine if and at what rate the influence of roentgen rays on isolated thymus cell nuclei corresponds with their influence on living organs. In this connection we were especially interested in indications concerning a reversible transformation of the desoxyribo and ribo radicals of the nucleic acids.

Indications of such a process seemed to be provided by the well-known investigations of CASPERSSON (25) and some observations of J. S. MITCHELL (26).

After roentgen ray irradiation *in vivo* of a carcinoma tissue, MITCHELL observed a significant increase in the ultraviolet absorption of the cytoplasm. According to MITCHELL »the increase in cytoplasmatic absorption produced by irradiation is of interest in relation to the cytoplasmatic absorption recently described (27) in growing tissues and attributed to pentose nucleotides. The absorbing material appearing after irradiation is not thymonucleic acid itself, as shown by the FEULGEN reaction, but at the wave-length 2537 Å, corresponds in absorption to that of, for example, a 2 per cent solution of nucleic acid. Thus the magnitude of the observed effect is certainly consistent with the possibility that the increased absorption may be due to purine and pyrimidine derivatives. Further, microchemical tests have shown that the increased absorption

is accompanied, at least in some cases, by positive pentose reactions in the cytoplasm.»

DAVIDSON and WAYMOUTH (28), reviewing MITCHELL's observations and adding a private communication from this author, emphasize MITCHELL's view »that ribonucleotides are formed in the cell from unknown precursors and are reduced to desoxyribonucleotides which are finally polymerized and deposited as desoxyribonucleic acid».

In what follows, some experiments will be described in which the influence of the irradiation on cell nuclei was studied. The effect of radiation on the chemical and physical properties of nuclear nucleoproteins and their components was followed by

1) estimation of P, N, desoxyribonucleic acid (by the Dische reaction and spectrophotometrically) and histone content (by the biuret reaction),
2) viscosity measurements,
3) determination of the dialysis rate and
4) adsorption analysis.

Experimental

Cell nuclei were prepared from fresh calf thymus according to the method earlier described (29). 500 g thymus tissue yielded 90 g moist cell nuclei. 45 g portions were irradiated with 25,000 r (CK 29—32) and 65,000 r[1] (CK 35) (tube voltage 155 kV; 1 Al). The temperature of the nuclei was kept at 0° during the irradiation. The control nuclei were also kept at 0°.

The further treatments of irradiated and control cell nuclei were carried out simultaneously and exactly in the same manner. The nuclei were dissolved by slowly adding 10 volumes M-NaCl solution with vigorous stirring and keeping the suspension thus obtained overnight in the refrigerator. The viscous solution was then centrifuged at 10,000 r. p. m. for 45 min. From the centrifugate the nucleoproteins were precipitated by the addition of 6 volumes of water. The precipitate was dissolved in 230 ml M-NaCl solution, reprecipitated with 6 volumes of water and finally dissolved in 200 ml M-NaCl. This solution was used for analysis and physico-chemical characterization.

Experiment CK 35 was performed in a similar way, but the nuclei were kept at 20° for 2 hours before being dissolved in M-NaCl.

I. Analytical Characterization of the Nucleoproteins.

For the estimation of N the micro-Kjeldahl method was used, while P was determined according to FISKE and SUBBAROW. The nucleic acid

[1] These doses are essentially higher than those used therapeutically and those used in the experiments on nucleic acid metabolism by HEVESY and EULER. It may be that the effect of such high doses is destructive to nuclei.

contents of the preparations were determined both spectrophotometrically[1] and by the diphenylamine reaction. As standard a nucleic acid prepared according to HAMMARSTEN was used. The diphenylamine reaction is influenced by the presence of proteins. The data obtained by this method for the nucleic acid content of the nucleoprotein preparations cannot be taken as absolute values. On the other hand, the method was adequate for determining whether any changes in the nucleic acid content of the nucleoproteins occurred during irradiation.

The orcin reaction was used for a further characterization of the irradiated and control nucleoproteins. This reaction is generally assumed to be specific for pentose (30). Experiments performed in this laboratory, which will soon be published (32), showed, however, that even desoxyribose reacted with orcin, giving a green colour with roughly one-tenth the intensity of that developed by ribose under the same conditions. The orcin reaction is thus inapplicable as a quantitative test for ribose in the presence of larger amounts of desoxyribose. The orcin reaction given by nucleoprotein preparations from cell nuclei can be assumed to be due, at least in part, to the desoxyribose present.

The protein contents of the preparations were determined with the biuret reaction. The determinations were performed in the following way: 1—3 ml of the solution was mixed with 2 ml 5 M-NaCl. 0.6 ml of a 0.5 per cent copper sulphate solution was then added and the volume of the mixture made up to 6 ml with M-NaCl. The colour developed was compared after 20 min. or more with that obtained with a standard clupein solution (in 1 M-NaCl) in a Zeiss step photometer using filter S 61. The relation between the concentration and the colour intensity is not linear and was therefore determined empirically.

Table 1.

Preparation	% N	% P	N:P	Nucleic acid		% Protein (expressed as clupein) (biuret reaction)	% ribonucleic acid.
				spectrophotom. %	Dische %		
CK 29 A	0.193	0.063	3.06	0.71	0.68	0.54	0.164
CK 29 B (irradiated)	0.166	0.057	2.91	0.73	0.64	0.69	0.148
CK 30 A	0.215	0.075	2.86	0.83	0.79	1.02	0.191
CK 30 B (irradiated)	0.217	0.076	2.86	0.77	0.78	1.12	0.187
CK 32 A	0.230	0.078	2.95	—	0.96	0.84	—
CK 32 B (irradiated)	0.222	0.078	2.85	—	0.90	0.87	—
CK 35 C	0.173	0.060	2.88	—	0.58	0.70	—
CK 35 D (irradiated)	0.178	0.062	2.87	—	0.57	0.85	—

[1] The spectrophotometrical measurements were carried out by Ing. BERTIL HÖGBERG.

As is seen from Table 1, no significant differences were found between the compositions of nucleoproteins prepared from irradiated and normal cell nuclei. Furthermore, the concentrations of the nucleoprotein solutions obtained from irradiated and normal nuclei were approximately the same. Taking into account that the purification of the nucleoprotein was carried out by making use of the characteristic precipitability of this compound on dilution of the solvent (M-NaCl) with water, we may conclude that a splitting of the nucleoprotein into its components by the action of the roentgen rays did not occur to any appreciable extent.

II. Physico-Chemical Characterization of the Nucleoproteins.

a) Viscosity Measurements.

The viscosity measurements were carried out in a Ostwald viscometer at $20 \pm 0.1°$. The results obtained are summarized in Table 2. In all experiments the viscosities of the irradiated nucleoprotein preparations were somewhat higher than those of the normal nucleoproteins. In view of the high sensitivity of the viscosity measurements, the differences obtained must be considered insignificant.

Table 2.

Preparation	N content	Undiluted solution c = 1	Relative viscosity		
			c = 0.5	c = 0.25	c = 0.125
CK 30 A	2.15 mg. g.	95.60	12.34	3.661	1.929
CK 30 B (irradiated)	2.17 »	129.80	14.53	4.065	2.008
CK 32 A	2.30 »	38.25	5.00	2.208	1.493
CK 32 B (irradiated)	2.34 »	41.59	5.32	2.303	1.518
CK 35 A	1.04 »	—	4.15	2.039	1.408
CK 35 B (irradiated)	1.07 »	—	4.59	2.168	1.459
CK 35 C	1.73 »	—	12.26	3.740	1.870
CK 35 D (irradiated)	1.78 »	—	12.50	3.795	1.899

b) Dialysis.

5 ml portions of the control nucleoprotein solutions were diluted with M-NaCl to 20 ml. The solution of the irradiated nucleoprotein was then diluted with M-NaCl to give the same viscosity as that shown by the diluted solution of the control nucleoprotein. 20 ml portions of these solutions were dialyzed through cellophane against 75 ml M-NaCl at 0°. The result of these experiments are seen in Table 3.

It has previously been shown that the protein component of nucleoproteins prepared from thymus nuclei contains an amount of low-molecular compounds (33). The dialysis experiments described above were

Table 3.

Preparation	% P dialyzed		% N dialyzed	
	16 hours	52 hours	16 hours	52 hours
CK 30 A	0.40	0.46	14.6	23.4
CK 30 B (irradiated)	0.43	0.54	18.7	25.8
CK 32 A	0.29	0.44	16.1	—
CK 32 B (irradiated).....	0.42	0.59	16.0	—

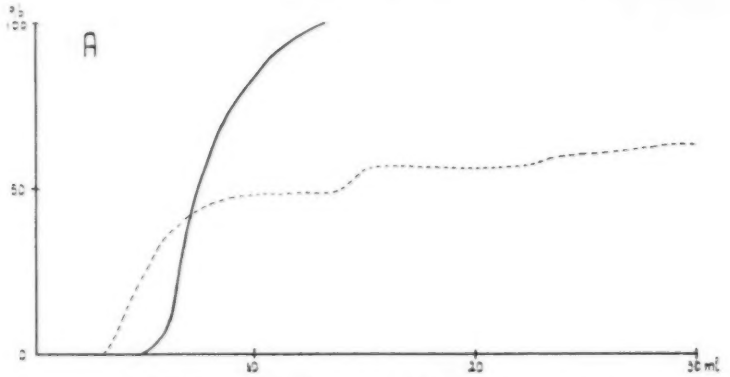
carried out in order to decide whether a depolymerisation of undialyzable or slowly dialyzing protein fractions took place under the action of the X-rays. In 16 hours about 15 per cent of the total N, *i. e.* about one third of the protein N of the normal nucleoprotein, passed through the cellophane membrane. In experiment 32, in which the nucleoproteins A and B were prepared strictly simultaneously and especial care was taken to keep the solutions at 0° during the preparation, the same value for the percentage of dialyzable N was found with both irradiated and normal nuclei. In experiment 30 somewhat more N dialyzed in the case of the irradiated preparation.

c) Adsorption Analysis.

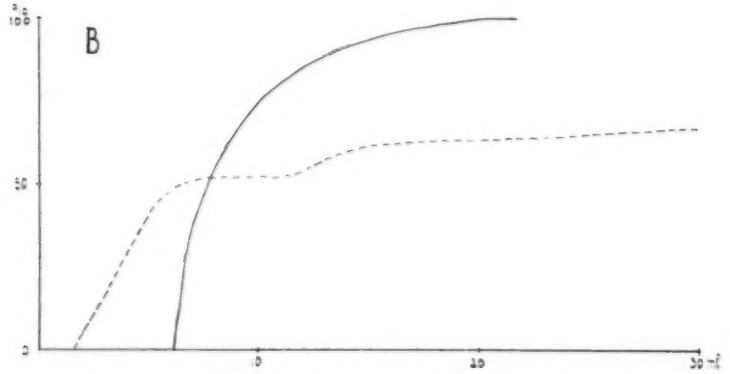
These experiments were carried out as described in earlier papers by the present authors (31). As adsorbents aluminium oxide (Merck puriss., treated with acetic acid) and floridin XS were used. The nucleoprotein solutions were diluted to 0.25 per cent. The solution leaving the adsorption column was continuously analyzed for nucleic acid by the method of Dische. For protein determinations the biuret reaction was used. As found earlier, the nucleic acid component separates from the protein component when solutions of thymus nucleoproteins are forced through a column of aluminium oxide or floridin, indicating that at least some of the nucleoprotein molecules contain loose, salt-like bonds between the acid and the basic protein. As is seen in Fig. 1, there is practically no difference between the behaviours of nucleoproteins obtained from irradiated and normal cell nuclei in adsorption analysis. Consequently, there is no experimental evidence indicating that any change in the nature of the bonds between nucleic acid and protein occurred during the irradiation.

On the Effect of Ultraviolet Light on Isolated Cell Nuclei.

In connection with the investigation described in the present paper an experiment on the influence of ultraviolet light on isolated thymus cell nuclei should be mentioned. The nuclei, the temperature of which was



A. CK 29 A, adsorbent: aluminium oxide, 3.94 ml.



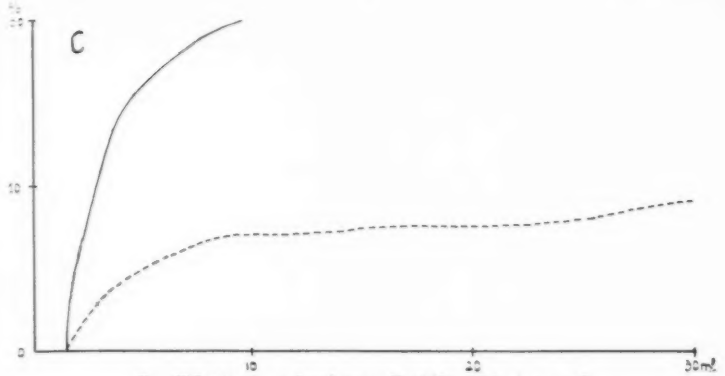
B. CK 29 B, adsorbent: aluminium oxide, 3.94 ml.

Fig. 1. Adsorption analysis of nucleoprotein

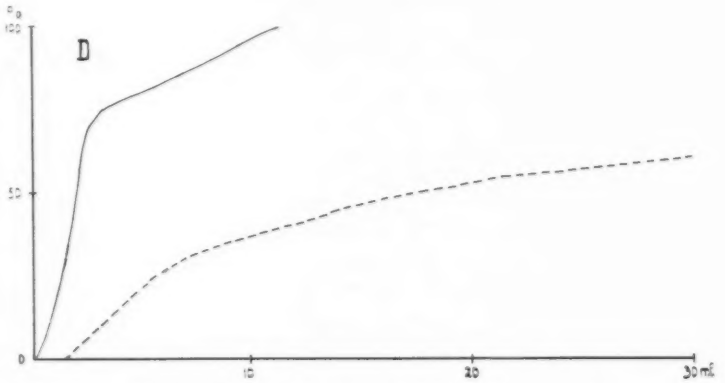
carefully kept at 0°, were irradiated for 30 min. with the ultraviolet light from a mercury quarz tube at a distance of 10 cm.

Then the nuclei were suspended in 1 M-NaCl and the viscosity of the *suspension* was measured in an Ostwald viscometer at different intervals. Control cell nuclei were treated in the same way. Both suspensions were kept at 0°. The viscosity measurements were performed at 20°.

After 12 hours the greater part of the nuclei were dissolved. The undissolved material was centrifuged off and the viscosity of the clear solution determined. There was practically no difference between the viscosity values obtained for irradiated and control cell nuclei, indicating



C. CK 29 A, adsorbent: floridin XS, 2.74 ml.



D. CK 29 B, adsorbent: floridin XS, 2.74 ml.

solutions CK 29 A and B (irradiated).

that no significant changes in the degree of polymerisation of the high-molecular components of cell nuclei took place during irradiation.[1]

Conclusions

In view of the fact, established by a series of investigations with labelled phosphate (12; 13; 18), that the nucleoprotein metabolism in normal and cancerous living tissues is inhibited by roentgen doses from

[1] In this connection it is of interest to recall the results arrived at by SVEDBERG and BROHULT (34). They found that haemocyanin molecules were split by ultraviolet light into two halves which were connected by a weak bond.

about 300 r, the effect of roentgen rays (25,000—65,000 r) on isolated cell nuclei from calf thymus was investigated. Nucleoproteins prepared from the irradiated and from non-irradiated cell nuclei of the same preparation were compared. The comparison was extended to the following properties:

1) chemical composition,

2) viscosity of solutions in M-NaCl, indicating the degree of polymerization;

3) dialysis rate, giving an indication of the molecular size of the protein component of the nucleoprotein;

4) the adsorption affinity for different adsorbents, indicating the ratio of dissociable and dissociated nucleoprotein molecules to their total quantity.

In none of these series of experiments could significant differences be found between the irradiated and non-irradiated nuclei.

Corresponding experiments were carried out on irradiated and non-irradiated calf thymus tissue, taken immediately after the killing of the animals. No effects of the irradiation could be detected in the extracts obtained from the irradiated and non-irradiated tissue.

From the experiments described above, we conclude that the roentgen doses used here are not able to produce changes in the chemical or physical properties of the nucleoproteins present in isolated cell nuclei. In this connection we may touch upon earlier experiments, not yet published, in which we failed to detect any transformation from desoxyribonucleic acid to ribonucleic acid by enzymic action *in vitro*. There is no evidence that the apparently simple oxidation of the desoxyribo radical, predominating in the nucleus, into the ribo radical, predominating in the cytoplasm, which cannot be performed by chemical means, is produced by irradiation. Regarding the depolymerization of the nucleic acid, the influence of the medium (pH, salt concentration) seems to govern the velocity of reaction and the equilibrium so completely that no other influence, even that of heavy roentgen doses, makes itself apparent.

On the other hand, the radio-stability of the cell nuclei shown by our experiments cannot be regarded as an indication that these cell nuclei had totally lost their biological activity during the careful isolation. Further experiments with »artificial cytoplasms» may permit a characterization of this activities.

We are indebted to Dr. ARNE FORSSBERG for his kind help with the irradiation of cell nuclei in the Radio-physical Institute, Caroline Hospital, Stockholm.

Our thanks are due to our collaborators HANS HASSELQUIST, MAIRE JAARMA, MARIANNE LUNDIN and ERICH SALUSTE for valuable preparative and analytical help.

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SUMMARY

In order to compare the physiological state of isolated cell nuclei with their state in a living tissue, nuclei carefully isolated from calf thymus at pH 4—6 were irradiated with 25,000 and 65,000 r. Nucleoproteins were prepared from the irradiated and non-irradiated nuclei and characterized by analysis and by viscosity, dialysis and adsorption measurements.

No significant changes due to the irradiation could be ascertained in the properties of the nucleoproteins. This result is, however, not regarded as an indication that the cell nuclei had totally lost their biological activity.

ZUSAMMENFASSUNG

Um den physiologischen Zustand von isolierten Zellkernen mit dem Zustand derselben im lebenden Gewebe zu vergleichen wurden Zellkerne, welche sorgfältig aus Kalbsthymus bei pH 4—6 isoliert worden waren, mit Röntgendosen von 25,000 resp. 65,000 r bestrahlt. Aus den bestrahlten und den nicht-bestrahlten Kernen wurden Nucleoproteide isoliert und durch ihre Zusammensetzung und Viscosität sowie durch Messungen der Dialysierbarkeit und Adsorptionsaffinität charakterisiert.

Kennzeichnende Veränderungen der Eigenschaften der Nucleoproteide, veranlasst durch die Bestrahlung, konnten nicht nachgewiesen werden. Dieses Ergebnis wird indessen nicht als Anzeichen dafür angesehen, dass die isolierten Zellkerne ihre biologische Aktivität vollkommen verloren haben.

RÉSUMÉ

Afin de comparer l'état physiologique des noyaux isolés avec l'état des noyaux contenues dans les tissus vivants, ces noyaux, soigneusement isolés du thymus de veau, ont été irradiés par des doses de rayons Roentgen de 25,000 r resp. de 65,000 r à pH 4—6. Nucléoprotéides furent préparés des noyaux irradiés et non-irradiés et furent characterisés par analyse, par déterminations de la viscosité, de la dialyse et de l'adsorption. Les propriétés des noyaux cellulaires n'ont pas été trouvées changées par l'irradiation. Toutefois ce résultat n'indique pas complètement que les noyaux cellulaires irradiés ont perdu leur activité biologique.

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FROM THE RADIOPHYSICAL OF KING GUSTAV V:S JUBILEE CLINIC, STOCKHOLM
(CHIEF: PROF. R. SIEVERT)

THE ACTION OF ROENTGEN RAYS ON THE ENZYME CATALASE[1]

by

Arne Forssberg

Introduction: The question how ionizing radiation acts on living organisms has been discussed almost ever since medical use has been made of roentgen rays and radioactive substances. Even if we limit the discussion to the cell-destructive action of therapeutic doses, say 1,000—5,000 r or so, no general agreement has been reached on the mode of action. Plainly, cells are more radio-sensible during some of their division phases, as on the whole in stages of high metabolistic activity, than in the resting stage. It may be presumed that this fact is of fundamental importance in radiotherapy. But these differences are generally not so pronounced as those often found between different organs, tissues, or species. An example will elucidate this statement. Dry, non germinant seeds of many cereals are retarded up to 50 % in their later growth by doses of 10,000 r or less, estimated by the weight or length of the plants some time after the roentgen treatment. In order to obtain the same effect on the dry seeds of many species of the Cruciferae plant-family, doses of from 100,000 to 500,000 r must be administered. If the seeds are soaked in water for 24 hours before they are irradiated, *i. e.* when the metabolism and the cell division has started, the same effect is obtained with somewhat smaller doses, but the relative radio-sensibility remains on the whole unchanged. Thus, except for the differences due to whether the cell is in rest or not, there exists a great variation in radio-sensibility even in organisms so nearly related as for instance seeds of different plants.

This points to a dissimilarity of another nature. It is conceivable that some biochemical difference might explain the fact. A great many biochemical processes, however, have been proved to remain remarkably uninfluenced even by high irradiation doses given *in vivo*. Enzymatic reactions for instance are often stated to be uninfluenced in organisms

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irradiated with modest doses. This statement is probably not quite correct, however, but partly a consequence of the way in which the analyses of the irradiation effects are performed (DALE (1)). These facts may be illustrated by an example.

The author (FORSSBERG (2)) investigated the roentgen-ray effect on the enzyme catalase, which as far as we know is present in all cells and indispensable to the normal function of the organism. If different animal organs or whole organisms are irradiated and the catalase activity determined afterwards in the usual manner, *i. e.* from a sample of the ground organ, no traces of inactivation could be found even at the »supratherapeutic» dose of 83.000 r. A diluted water solution of pure crystalline enzyme, on the other hand, turned out to be highly radio-sensible. The picture is complicated by the fact that the inactivation is a function of the radiation intensity as described below. For the present discussion it is, however, sufficient to state that doses of 100 r or less will cause a strong inactivation when the enzyme is pure. This great change in radio-sensibility is c'early due to environmental factors. The catalase may be said to be highly »protected» from roentgen rays in its natural cell environment.

For details the reader is referred to the work quoted. In short, the roentgen-ray inactivation of the pure enzyme can be shown to be more or less protected by small amounts of added proteins or other substances. This protection is partly or wholly counteracted in the presence of salts. The irradiation effect furthermore depends on a number of other factors of the irradiated medium, *e. g.* pH. Some of these factors may even enhance the roentgen ray effect. It is thus possible to vary the radiosensibility of the enzyme within wide limits by rather small alterations in the composition of the irradiated solution. Differences of this kind in the chemical composition of the cells may actually exist. In addition to the cell division activity *per se* as a factor of importance to an understanding of the action of ionizing rays, we may also possibly consider those circumstances. We may consequently form a conception of the radio-sensibility of an organism according to wh'ch a vital constituent, *e. g.* the catalase molecules in this example, is almost completely protected in the greater part of a cell, but highly radio-sensible in other, and maybe vital, parts of it.

Before proceeding any further, it is appropriate to deal with some points in the discussion of the action of ionizing rays on living matter and on solutions of chemical substances. One problem of radiobiology is the question whether the action of ionizing rays is *direct*, as assumed in the »hit theory», or *indirect* — in the literature sometimes referred to as a »radiochemical» action. The difference may be illustrated by a survey of some experimental results.

The conceptions summed up in the hit or target theory and its applications in experimental radiobiology have been summarized by numerous authors (LEA, HAINES and COULSON (3), JORDAN (4), ZIMMER (5) and others). The action is according to these ideas due to the statistically calculable distribution of ionizations within a »sensible spot» of the irradiated organism. Plotting the effect against the dosage we get an exponential curve for the simplest assumption that the effect is produced by a single ionization, and more or less S-shaped curves if two or more ionizations are assumed to be necessary to produce the given effect.

The confrontation of the biological experiments with this theory gives a somewhat confused impression. Actually, the irradiation of bacteria and similar relatively undifferentiated organisms often fits the hit theory well, assuming that a single hit kills the organism. It must also be admitted that the biological view, *i. e.* the assumption that the dosage-effect curve is explained by a widely varying radio-sensibility of the individuals of the population, is very unlikely in this case, as a distribution of the radio-sensibility according to an exponential curve would be almost inconceivable. Such small organisms may possibly then be killed by a single ionization in a vital part.

But even the upholders of the hit theory are doubtful of its applicability to the experimental results in more complicated cases. ZIMMER (5) has summarized the work up to 1942. A survey of the material shows curves explained on the assumption that up to 39 hits are necessary to kill the organism and in one case — the killing of eggs of Drosophila — curves explained on the assumption that the effect is produced by from one to six hits at different stages of development. A drawback of the hit theory is that the formulas derived do not consider the possibility of recovery from the radiation insult or the influence of reversible reactions. But admitting this, it is difficult to understand how the biological curves can be correctly interpreted by the theory.

As for the results of irradiations on chemical substances, some investigations may be quoted which indicate a simple monomolecular constant in roentgen ray action. The destruction (»inactivation») of pepsin and trypsin (HUSSEY and THOMPSEN (6); CLARK and NORTHROP (7)), as well as the decomposition of oxyhaemoglobin (FRICKE and PETERSEN (8)), are described through the formula: $\frac{N_1}{N_0} = 1 - e^{-kD}$. ($\frac{N_1}{N_0}$ = the fraction denoting changed molecules.) The same was found by ZIMMER in transforming white phosphorus into red when irradiated in benzol. In all these cases there seem to be good reasons to assume that the reaction proceeds after a direct hit on the molecule, and without any participation of the solvent.

In many cases, however, the yield of changed molecules increase linearly with the dose (oxidation of $FeSO_4$, FRICKE and MORSE (9); reduction of $K_2Cr_2O_7$, FRICKE and BROWNSCOMBE (10); decomposition of H_2O_2, RISSE (11), and $K_2S_2O_8$, GLOCKER and RISSE (12). Particularly FRICKE's and MORSE's investigation of the reaction $FeSO_4 \xrightarrow{\text{roentgen rays}} Fe_2(SO_4)_3$ gives a certain insight in the mechanism. Their results may be summarized as follows.

1) In a concentration interval 1—20 the dose required to oxidize 1 mol of ferrosulphate was constant ($= 5.5 \times 10^7$ r).

2) The reaction proceeds linearly up to the critical dose, and from then on at a slower but still constant speed. The critical dose is characterized as follows: the absolute amount of ferrisulphate formed is equivalent to the free oxygen in the solution.

These results do not agree with the assumption that the transformation takes place after direct hits on the molecules. Assuming the latter, one would expect exponential or S-shaped dosage-effect curves. Moreover the proof that the yield is within certain limits independent of the concentration is evidence of an interaction with the water or some hypothetical transformation product of the water, *e. g.* H_2O_2 as the content of gaseous O_2 in the solution is evidently significant in this case. This mode of roentgen ray action is called indirect.

The difference between direct and indirect action may be said to be wholly academical and of no biological importance, since in cases of indirect action the primary moment will also be an ionization or activation of a molecule followed by a transmission of energy to the investigated component. Considering, however, that 1.000 r will produce an average of only some 10^{15} ion pairs per cm^3 of tissue or water solution, the chances of direct hits on a given kind of molecules, which may even be present in a low concentration, are very small. On the assumption of indirect action this difficulty will partly disappear, especially when, as in FRICKE's case, water may be postulated to be a likely acceptor of the primary absorbed energy.

Experimental: The present investigation provides further details of the reaction mechanism in the inactivation of catalase. Owing to the obvious complexity of the problem, the discussion should be limited to the action on the pure enzyme under a few defined conditions.

The enzyme preparation used throughout the investigation was a crystalline beef-liver catalase of the activity »Kat. f.» = 29,700. This implies a very pure enzyme (SUMNER (13)). A special difficulty was the natural inactivation of the enzyme when strongly diluted, which at first made a quantitative estimate of the results uncertain on account of the variable chances of the molecules to be inactivated by roentgen rays.

Most of these difficulties were overcome by a cautious and gentle solution of the crystals and subsequent dilution: 0.1 ml of a suspension of catalase crystals containing 6.32×10^{-4} g. enzyme, was added to 2.9 ml. icecooled phosphate puffer, pH = 7.4, and 0.15 g. NaCl added successively while shaking. The crystals were left to dissolve at 0°, which generally took 24—48 hours. Dilutions were made immediately before the irradiation by adding phosphate puffer slowly to the dissolved catalase-crystals. The final concentration of the irradiated samples was then: 4.21×10^{-7} g. catalase per ml. in a medium of 1/30 mol phosphate puffer, pH = 7.4, and 1×10^{-6} % NaCl. The solutions were saturated with air, except in the experiments dealing with the effects of different gases. Moreover, a 300 times more concentrated enzyme solution containing 0.61 % NaCl was prepared, otherwise like the first. The distilled water used was of a purity $\sim 1—2 \times 10^{-6}$. In this way almost stable enzyme solutions could be obtained. The loss of activity under the most unfavourable conditions, *i. e.* when the more diluted enzyme solution was kept at 20° in O_2 atmosphere, was about 10 % in two hours. A small correction had accordingly to be applied in experiments lasting so long. At 0°, the temperature at which the experiments here were made, the stability was even better. Series, which occasionally showed greater inactivation in the controls, were discarded. It is of general interest to note that in N_2 and H_2-atmospheres even the diluted enzyme solution was more stable.

A corresponding correction for loss of activity during freezing with carbonic acid snow (Page 11) could be made after the loss of activity in the unirradiated samples had been determined. In this case no appreciable loss of activity was found while the enzyme sample remained frozen, but a certain number of enzyme molecules were destroyed the moment the liquid became solid.

The samples were irradiated in closed vessels of »Neutral Glass»; the amount of solution being 5 ml. in a 5 mm. deep layer. Unirradiated samples were always run parallel with the experiments. The intensity of the roentgen rays was checked occasionally by means of calibrated condenser-chambers. The samples were irradiated with a Metalix therapy tube connected to a Stabilivolt apparatus (4 mA, 155 kV; filtration 1 Al) at varying intensities. The relatively hard radiation ensures a practically uniform irradiation of the 5 mm thick layer. The doses are expressed in number of ions formed; as a basis was taken the generally accepted figure: 1,000 r = 1.61×10^{15} ion pairs per ml. of water. The catalase concentration in the irradiated samples and the amount of inactivation are given in molecules per ml. SUMNER states the molecule weight of beef-liver catalase to be $\sim 228{,}000$, calculated from ultra centrifugal tests. The correctness of the values given below depends on the degree

of purity of the crystalline enzyme. Any small impurity will reduce all the figures a trifle.

Inactivation of enzyme solutions of different concentrations. Attention must once more be called to the fact that the experiments in this and the following section were performed in air-saturated solutions. They were repeated 4—6 times. To show the degree of accuracy, the results at the higher concentration have been tabulated in Table 1. The results are also plotted in Fig. 1 (○). A general discussion of the curves will be attempted in a later section, when the whole experimental material has been presented. From the points of view given in the introduction a purely formal treatment gives the following results: When the enzyme concentration is as high as 3.4×10^{14} molecules per ml. the inactivation curve is fairly well described by the formula: $\frac{N_1}{N_0} = 1 - e^{-kD}$ over the whole investigated range. A logarithmic plotting of the results shows, however, that the straight line does not intersect the y-axis at the point 100. This indicates rapid inactivation at the very onset of the irradiation. But apart from this deviation, which seems to disappear at still higher enzyme concentrations in the irradiated solution, the reaction proceeds up to complete destruction of the enzyme in a way, which according to the above is described by the hit theory on the assumption of one direct hit on every catalase molecule, and without the participation of any secondary reactions.

The results of the irradiation of a 300 times more diluted enzyme solution show, however, another picture. After an initial rapid inactivation amounting to some 10 %, the course of the reaction follows the relation: $\frac{N_1}{N_0} = 1 - kD$ (Fig. 1 (×)). This means a likely participation of water in the reaction, as the inactivation proceeds linearly with increasing roentgen doses. So far according to the current views.

A few experiments with intermediate concentrations indicate a graded transition between the two modes of action. We may thus say that there are no sharp distinctions in the reactions, and the fact that the experimental results fit one or the other formula must be accidental. Later it will be shown that the mode of action is a complicated function of the concentration of the irradiated enzyme, of the intensity of the irradiation, and of the gas-content of the solution.

The different slopes of the curves at the two concentrations makes an exact comparison of the yield of inactivated molecules per ion pair formed impossible. If, however, this figure is estimated from the experiments with the higher concentration and for a dosage giving 50 %

Table 1

Enzyme concentration: 3.43 × 10^{14} molecules per ml., intensity: 1 030 r/m. Temp. 0°.

Dose, ion pairs/ml.	Inactivated molecules/ml.	Inactivated molecules per ion pair by 50 % inactivation.
3.32 × 10^{15}	0.47 × 10^{14} ± 2.1 %	
8.30	0.55 ± 1.8 %	
33.2	1.44 ± 0.70 %	
66.4	2.04 ± 1.0 %	$\infty \frac{1.72 \times 10^{14}}{46.5 \times 10^{15}} = 3.7 \times 10^{-3}$
99.6	2.49 ± 1.0 %	
149.0	2.96 ± 0.97 %	
199.0	3.20 ± 0.42 %	

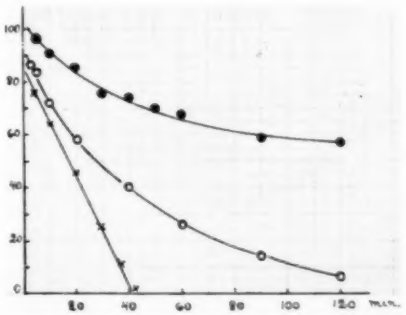

Fig. 1. Enzyme conc. 3.43 × 10^{14} molecules per ml.; intensity 1,030 r/m (○). Enzyme conc. 1.12 × 10^{12} molecules per ml.
a) intensity 8.0 r/m (●).
b) intensity 1,030 r/m (×).

Ordinate in all figures; percentage not inactivated molecules.

inactivation we get 3.7×10^{-3} in comparison with the constant value 1.4×10^{-5} at the lower concentration. The ratio 265 is close to the concentration ratio 300.

The action of roentgen rays of varying intensities. In the author's previous communication it was shown that the effect per dosage unit was much higher at lower intensities, at least for shorter irradiation times. Similar results of irradiations of biological objects seem to be rare if they occur at all. To explain them we can assume that the organism passes through repeated stages of high radio-sensibility; the chances of hitting such stages would then increase with the length of the irradiation. The opposite result, which is rather common in radiobiology, viz. greater effect at higher intensities, is accounted for by the assumption that a reversible reaction or some sort of recovery will partly counteract the effects of prolonged irradiations at low intensities.

When the irradiated system is so comparatively simple as the one discussed here, however, one would hardly expect the results actually

Table 2

Intensity r min.	Irradiation time in min.	Increase of intensity, times.	Molecules inactivated per ion pair.	Increase in effect at the lower intensity, times.	Average increase when reducing the intensity.
0.023	330	5.0	3.24×10^{-2}	3.5	$\frac{3.5}{5.0} = 0.70$
0.116	330		9.38×10^{-2}		
0.464	60	4.2	4.92×10^{-3}	3.00	$\frac{3.00}{4.2} = 0.71$
1.95	60		1.64×10^{-3}		

obtained, and their occurrence would indicate some sort of secondary reaction. In the comments on the results given in my previous paper, the slopes of the curves were presumed to be at least partly explained by the assumption of a reversible reaction. But it was afterwards possible to show that under conditions of these experiments no measurable reversible formation of active enzyme took place during the short times (max. 2 hours) the experiments lasted; at higher enzyme concentration, and after longer times, such reversibility is, however, easy to prove under certain conditions.

In Fig. 1 the beginning of the inactivation curve at the intensity 8.0 r/m is plotted for a comparison with the curve at 1,030 r/m. Up to an irradiation time of about two hours the inactivation proceeds at a rate approaching that of a monomolecular reaction. But from there onwards the inactivation is very insignificant, and seems to proceed linearly judging by a few experiments not included in the graph.

A closer study of the inactivation curve at the intensity 1,030 r/m in very short irradiation times reveals a start of the reaction identical with that at the lower intensity. The transition to a linear rate occurs after about 1 minute's irradiation. The dosages in the two cases are accordingly approximately equivalent when the reaction passes over to a linear rate.

The fact that the effect increases with decreasing intensity up to a certain dosage may be of importance to an understanding of the biological effects of low intensities, possibly even of such very low intensities as the natural radiation. To that purpose we must also assume the enzyme to be partly present in the cell in a highly sensitive state, *i. e.* not protected. This remains unproven. However, it is interesting to note that the effect increases steadily with decreasing intensity as far as investigated (Table 2). Owing to the natural decay of activity, which becomes easily measurable after 6 hours, the investigation could not be followed up to still lower intensities. The maximum decay of activity without any irradiation amounted to 17 % in 6 hous; this was corrected for. Owing to the

uncertainty of this correction, and because of the fact that the shapes of the curves at these low intensities are unknown, we may consider the figures in Columns 4 and 5 merely giving an approximate estimate of the increase in roentgen-ray effect at lower intensities. The same objection is relevant to the experiments in Table 3. From these figures and from the estimated yield of $\sim 3 \times 10^{-2}$ inactivated molecules by the lowest intensity per ion pair we may presume that the yield: one inactivated molecule per ion pair formed in the irradiated solution may be possible at still lower intensities.

Inactivation and gas concentration of the solution. In the introduction investigations were discussed, which pointed to some cooperation of intermediate irradiation products of the water in the transformation of dissolved substances. The inactivation of catalase, at least under certain conditions, also appears to indicate the same mode of action. Complications are to be expected in this very case, as the irradiated substance is an enzyme which will split H_2O_2. In that case, the contents of gaseous O_2 and H_2 in the irradiated solution might well be of importance. This was confirmed by further experiments.

An enzyme solution containing 4.5×10^{12} molecules per ml. was saturated at 0° with a) O_2, b), H_2, c) N_2. The nitrogen and hydrogen were freed from oxygen by alcaline pyrogallol. The experiments were run as follows: 6 ml. of the enzyme solution were allowed to be bubbled through in gas-tight glass tubes for 30 minutes with a rapid flow of gas. This treatment will cause a small loss of activity (usually not exceeding 5 %). 1 ml. was then extracted from the tubes with the aid of the gas-pressure to determine the activity before the irradiation. Immediately afterwards the glass tubes were irradiated at 615 r/m (Fig. 2) and 8.0 r/m (Fig. 3). Owing to the small absolute inactivation only the beginning of the curves could be obtained at 8.0 r/m; the principle is, however, evident.

In order to present the results at 615 r/m in a form convenient for the discussion, the inactivation has been plotted against a dosage-unit $\frac{D}{D^1/_2}$, where $D^1/_2$ corresponds to 50 % inactivation. The curves thus intersect at the values $y = 50$ and $x = 1$, and the differences in their slope can be more accurately determined. This was done because the differences in action are not so pronounced at the higher intensity.

Speaking generally, the results give additional and more direct support to the hypothesis that the medium cooperate in the inactivation process. The reaction is clearly a rather complicated function of the irradiation intensity, of the concentration of the enzyme, and of the gas content in the solution. Now, since the roentgenrays split a certain number of water molecules it is conceivable that the same reactions would proceed

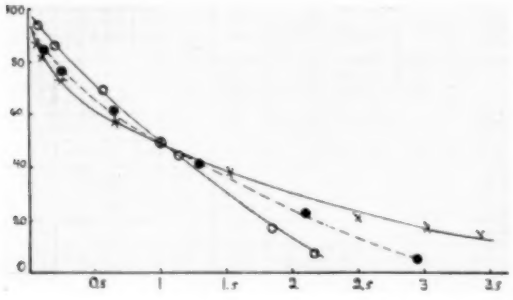

Fig. 2. ○ = O_2; ● = N_2; × = H_2. Abscissa: $\frac{D}{D^1/_2}$. Intensity: 615 r/m.

on a reduced scale, even in a medium which from the start holds no O_2 or H_2. The intermediate N_2-curves visualize such an event. The difference in action when the enzyme is irradiated in a saturated solution of O_2 or H_2 is marked, not only quantitatively, but also in the slope of the curve. This latter fact indicates a different mode of action. In order to get a quantitative conception of the mechanism of reaction, more detailed investigations are required, but the results so far obtained throw light upon some features.

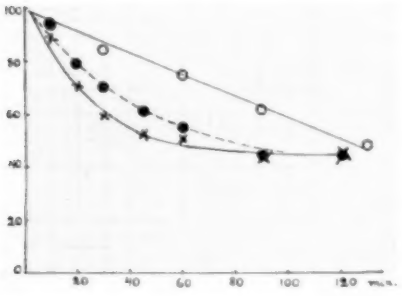

Fig. 3. Intensity: 8.0 r/m. Gases denoted as in Fig. 2. Abscissa: time in min.

In the discussion of the roentgen-ray action upon the water, it has been postulated that the molecules would split and partly reunite again under a momentary or more permanent formation of OH- and H-ions, H_2, and H_2O_2.

Besides the hydrogen peroxide, both the H_2 *in statu nascendi* as well as the OH- and H-ions may be suspected of taking part in the reaction with the enzyme. This implies various possibilities. Only a few points may be stressed. In an O_2-saturated enzyme solution there should be increased chances of a formation of peroxide, and a tendency — so far as the concentration of O_2 in the solution is still in excess — to a linear increase of the amount of H_2O_2 participating in the reaction.

In fact, in alcaline O_2-medium the inactivation proceeds at a clearly linear rate at least up to an irradiation time ~ 2 hours at the intensity 8.0 r/m. At irradiations of higher intensities one would expect deflections from the linear to appear as the excess of O_2 gradually disappears. The O_2-curve at the intensity 615 r/m also shows distinct deviations from the linear relation between dosage and effect on an earlier stage. Clearly, it is also the relation of the enzyme and O_2 concentrations which mainly determinates the slope of the two curves at the intensity 1.030

Table 3

Number of molecules in the irradiated solution: 6.9 × 10¹¹, temp. = — 80°. Air-saturated solution.

Intensity r/min.	Irradiation-time, min.	Increase of intensity, times.	Inactivated molecules per ion pair × 10^{-6}.	Increase in effect, at the lower intensity, times.	Average increase when reducing the intensity.
0.78	60	10.3	450	3.2	$\frac{3.2}{10.3} = 0.31$
8	60	17.1	140	6.4	$\frac{6.4}{17.1} = 0.37$
137	40	7.5	22	3.1	$\frac{3.1}{7.5} = 0.41$
1,030	20		7.0		

r/m in Fig. 1. The predominantly linear reaction rate at lower concentrations indicates that most of the molecules react according to the O_2-scheme in Fig. 2 and 3. So far the curves show plausible features. But there is also a reaction in a H_2-saturated solution, and if the irradiation time is not too long the quantitative yield is in this case moreover greater than in an O_2-saturated solution. It seemed possible that the slope of the H_2-curves may indicate a complex reaction. The rather sharp transition to a reaction rate with very slow enzyme inactivation, especially noticeable at the intensity 8.0 r/m, should then correspond to a consumption of the dissolved H_2. One would then expect that a renewed saturation with H_2-gas, *c. g.* after 45 min. irradiation, followed by continued irradiation should cause a more rapid subsequent inactivation. Repeated tests failed, however, to show anything but a very slight and probably insignificant increase in the reaction rate. The part played by the hydrogen gas in the reaction therefore seems rather obscure. One of the main features of the reaction is its dependence on the intensity and this dependence remains on the whole unchanged even when the gaseous content of the solution is varied.

Provided that the inactivation proceeds via secondary reactions between the enzyme and the medium, changes of temperature may influence the yield. Only a few experiments may be given here.

It is possible to freeze the enzyme solution by means of carbonic acid snow and melt it again with a fairly constant loss of activity for which correction could accordingly be made. Preliminary irradiations of the enzyme in a solid state were then made parallel with these at 0° (Table 3).

Compared with the figures in Tables 1 and 2, the results of irradiations in a solid state at about — 80° indicate that the yield per pair of ions is reduced. But the most conspicuous feature of the reaction mechan-

ism, the steady increase of the yield at lower intensities, remains on the whole unchanged. The results seem to imply that the whole reaction must proceed predominantly in the immediate vicinity of the enzyme molecule, unless we postulate some sort of conduction of energy in the solid state.

Further investigations on these problems have been started. The work was aided by a grant from »Konung Gustav V's Jubileumsfond». The author acknowledges with pleasure the cooperation of Mrs. Brita Widjer in the investigations.

SUMMARY

Contrary to earlier conceptions, enzymes are found to be highly radio-sensible under certain conditions. The composition of the medium surrounding the molecules is of paramount importance to the radio-sensibility of the enzyme catalase investigated. All stages from complete stability of the enzyme after doses of $\sim$ 100,000 r., to marked inactivation after doses of 5—10 r may be found after slight variations of the irradiated medium.

In this communication the mechanism of the roentgen-ray inactivation of the water-solved pure enzyme is especially investigated. Evidence is given of a complicated interaction of irradiation products of the water and the gases in the solution. The reaction proceeds in different ways according to the intensity of the radiation and the concentration of the enzyme.

ZUSAMMENFASSUNG

In Gegensatz zu den bisherigen Anschauungen hat man neuerdings gefunden dass Enzyme unter besonderen Bedingungen sehr röntgenstrahlenempfindlich sind. Von ausschlaggebender Bedeutung ist hierbei die chemische Zusammensetzung der das Enzym enthaltende Lösung. Dies war auch der Fall bei dem vom Verfasser untersuchten Enzym Katalase. Alle Stufen der Strahlenempfindlichkeit waren nachweisbar, von vollständiger Stabilität des Enzyms nach Dosen von 100,000 r. bis zu deutlicher Inaktivierung nach Dosen von nur 5—10 r. Diese Veränderungen in der Stabilität erscheinen nach ziemlich unbedeutende Variationen in der bestrahlten Enzymlösung.

In vorliegender Arbeit ist der Mechanismus der Röntgenstrahlen-Inaktivierung des im Wasser gelösten, reinen Enzyms zum Gegenstand einer Untersuchung gemacht worden. Es werden experimentelle Belege dafür gegeben dass Bestrahlungsprodukte des Wassers und darin gelöste Gase bei der Reaktion mitwirken. Die Reaktion verläuft dabei verschiedenartig, je nach der Intensität der Strahlung und der Konzentration des Enzyms.

RÉSUMÉ

Contrairement aux idées précédemment admises, il est apparu que les enzymes sont très sensibles au rayonnement dans certaines circonstances. La composition chimique de la solution d'enzyme soumise au rayonnement est d'une importance décisive, également en ce qui concerne l'enzyme catalase ici étudiée. Tous les stades, depuis la complète stabilité de l'enzyme après des doses de $\sim$ 100,000 r jusque'à une mise en inactivité marquée après des doses de seulement 5—10 r, peuvent être observés

lors de modifications relativement insignifiantes de la solution d'enzyme soumise au rayonnement.

La présente étude traite du mécanisme de la mise en inactivité de l'enzyme pure, délayée, sous l'effet des rayons Roentgen. L'idée que les produits provenant du rayonnement de l'eau et des gaz dissous dans l'eau contribuent aux réactions est confirmée par l'expérience. La réaction se passe alors de différentes manières suivant l'intensité du rayonnement et la concentration de l'enzyme.

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FROM THE ROENTGENDIAGNOSTIC DEPARTMENT OF THE COUNTY HOSPITAL, LANDSKRONA
(CHIEF: G. FORSSMAN, MED. LIC.)

3 CASES OF SKELETAL CHANGES ROUND THE KNEE JOINT IN PARATYPHOID FEVER IN INFANTS[1]

by

Gösta Forssman

It is a well-known fact that skeletal changes may occur as complications in typhoid fever. KRAUSE found 104 cases of bone changes in a material of 9,400 typhoid fever convalescents. The changes were localized as follows:

Thorax: 40 cases; leg: 32 cases; vertebrae: 13 cases; forearm: 8 cases; over-arm, foot, and jaw: 3 cases each; pelvis: 2 cases; scapula: 1 case.

KRAUSE classifies the bone changes in the following way:

I. Periostitis posttyphosa simplex

II. Ostitis posttyphosa
   a) Ostitis simplex without any marked periostitis
   b) Ostitis simplex with more pronounced periostitis

III. Osteomyelitis posttyphosa
   a) Osteomyelitis simplex with spontaneous regeneration
   b) Osteomyelitis simplex with sequestrum formation and highly productive periostitis
   c) Osteomyelitis simplex with mixed infection

As is the case in typhoid fever, suppurations occur in parathyphoid fever, too. PICK (1918) draws attention to the fact that the parathyphoid bacilli have a greater capacity to elicit suppurations than the typhoid bacilli. Abscesses in the spleen, the kidneys, liver and lungs are thus described i. a. by MARTENS (1920).

Isolated cases of suppurative monoarticular arthritis have been described in the literature. FEDOROJEFF (1927) reports two cases of suppu-

[1] Lecture at the Nordvästra Skånes Läkareförening Sept. 2, 1945, and at Svensk Förening för Medicinsk Radiologi Sept. 29, 1945; submitted for publication, Jan. 28, 1946.

rative arthritis in the shoulder joint; both cases recovered rapidly after repeated punctures. Parathyphoid bacilli were isolated from the punctate. — LANGVILL (1921) describes an 11 months old girl, who during one week had a fluctuating swelling in the shoulder joint accompanied by pains when moving, but without any oedema or redness. A thick yellow pus, containing paratyphoid bacilli type C, was removed by a small incision anteriorly. Drainage tube. Rapid recovery and freedom from symptoms after 5 weeks. — DOELLMAN (1915) describes one case of hydrops genu paratyphosus in an infant. LEWIS (1927) discusses a 14 months old girl, whose left knee swelled; no other symptoms were observed. An enormous amount of leukocytes + paratyphoid bacilli type B were isolated from the thick exudate. Blood test positive for type B paratyphoid fever. The knee healed rapidly. — Spondylitis after type B paratyphoid fever is also described, viz. by LYON (1917). — No roentgenograms of these cases have been published.

In Sweden TILLGREN and TROELL (1913) published one case of arthritis paratyphosa tarsi. A 6-year-old boy, who had had a severe paratyphoid general infection (blood test positive for type B paratyphoid fever) recovers apparently, but 6 weeks after the onset of the disease an acute suppurative arthritis develops in the left foot. The symptoms are not alarming, only moderate fever with oedema and redness on the back of the foot. 2 weeks after the onset of the symptoms in the foot incision of a fluctuating abscess with thin gray-yellow pus from the joint between os naviculare and os cuneiforme III. Culture of the pus yields paratyphoid bacilli type B. A roentgenogram taken 3 weeks after the incision shows atrophy of the whole foot skeleton but no focal destruction. Slow healing; freedom from symptoms 2 months after the operation.

After having had the opportunity, in the spring of 1945, of examining roentgenologically three cases of skeletal changes at and around the knee joint (osteitis + periostitis) in type C paratyphoid fever in refugee infants, I went through the great patho-anatomical and roentgenological text-books without finding any reference to this particular complication.

As similar cases seem to be but little known at least in Sweden, as, with the exception of the above-mentioned Swedish case, no roentgenologically examined cases are to be found in the available literature, as the roentgenograms in all the three cases were very similar — the changes always being localized at or around the knee joint —, as the roentgenological findings were the primary reason why a bacteriological investigation came to be performed and the presence of type C paratyphoid bacilli detected (see table), and as, finally, the course of healing has been studied clinically and roentgenologically in all the three cases until they were free from symptoms, which happened within 2—3 months even

when there had been severe bone destructions (case 2), I think that a short report on these cases might be of some interest.

Table showing the occurrence of Salmonella paratyphi

	Case 1	Case 2	Case 3
Abscess Pus	—	C	—
Blood	C	B + C	B + C
Faeces	—	—	C
Urine	—	—	—

Case 1. J. M. Born $^{11}/_{1}$ 1945.

Admitted to the Pediatrical Dept. $^{3}/_{5}$ 1945. Had for one month had a jumping fever with swelling of the left knee, now in subsidence, however.

State on admission: Good general condition. Weight 4,150 g. Jumping subfebrile temperature. No diarrhoea. Left knee: Extension defect 20°. Normal flexion. Slight swelling of the knee joint and of the left thigh. Abdomen 0. Blood counts: Haemoglobin 71 %, erythrocytes 3,700,000, leukocytes 10,400. Differential calculus shows a lymphocytosis of 75 %. Wassermann reaction negative in mother and child.

Roentgenogram $^{8}/_{5}$: Coffee-berry-sized bone destruction in the tibial metaphysis surrounded by sclerotic bone. The focus extends towards the epiphyseal cartilage. The epiphyseal nucleus is decalcified and smaller than in the sound knee. Large periosteal deposits on both the tibial and the femural diaphyses. — I suspected at first syphilis, but the WR was negative. — When an exactly similar case was admitted about a week later (case 2) the diagnosis paratyphoid fever became clear.

$^{23}/_{5}$. The swelling in the knee has disappeared and the extension defect diminished.

Roentgenogram $^{23}/_{5}$. The destruction within the left upper end of tibia is now more clearly outlined and filled out, which indicates regression. The femural and tibial periostites are unchanged since $^{8}/_{5}$. Small periosteal deposits on the upper part of the right ulna and radius.

Roentgenogram $^{4}/_{6}$. Regression. Increased sclerotization round the by now pea-sized destruction. The periostites, too, have diminished.

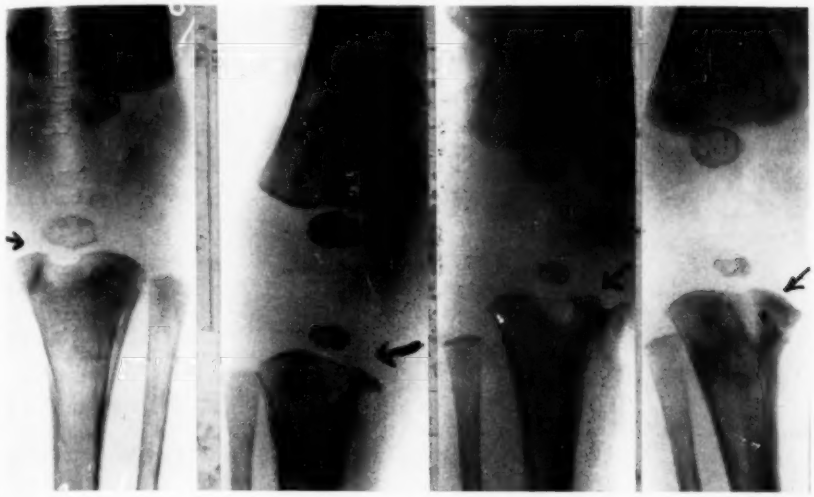
$^{7}/_{6}$. Blood: Positive Widal reaction for type C paratyphoid fever H $^{1}/_{10}$. Faeces and urine negative.

Roentgenogram $^{25}/_{6}$. Further regression with filling out of the cavity and, according to a roentgenogram taken $^{7}/_{8}$ 1945, the osteitis has healed; the patient is by now free from symptoms.

Case 2. H. H. Born $^{1}/_{3}$ 1945.

Admitted to the Pediatrical Dept. $^{5}/_{5}$ 1945 in an emaciated state, with pyoderma and scabies. Repeated incisions were performed because of widespread multiple dermal abscesses and suppurating lymph nodes in the axillae and the neck. Jumping fever. Diarrhoea. $^{22}/_{5}$. In the preceding 24 hours a plum-sized tender fluctuating abscess had appeared just below the right knee and anteriorly. Temp. 37°. Severe anaemia.

Roentgenogram $^{22}/_{5}$: Immediately up to the epiphyseal cartilage in the right upper tibial metaphysis there is a pea-sized diffusely outlined destruction cavity in the bone. The medial upper corner of the tibia is fractured and pressed downwards. Large periosteal deposits on the upper half of the tibia. Exteriorly an abscess in the soft parts. — The rest of the long bones normal. There is thus an acute inflammatory bone destruction in the upper tibial metaphysis with periostitis and an abscess in the soft parts. — As the appearance of the changes and their localization corresponded exactly to the findings in



Case 1. Case 2 a Case 2 b Case 2 c.

Case 1 ($^{3}/_{5}$ 45). Coffee-berry-sized bone destruction in the tibial metaphysis surrounded by sclerotic bone. Large periosteal deposits on both the tibial and the femural diaphyses.

Case 2 a. ($^{22}/_{5}$ 45). In the tibial metaphysis a pea-sized diffusely outlined destruction cavity in the bone. Large periosteal deposits on the upper half of the tibia. Exteriorly an abscess in the soft parts.

Case 2 b. ($^{1}/_{6}$ 45). Increased destruction, now encompassing the whole upper part of tibia from the epiphyseal line and 3 cm downwards. A 4—5 cm long periosteal deposit.

Case 2 c. ($^{25}/_{6}$ 45). Regression. $^{17}/_{8}$ 45. The process is healed.

case 1, it was suggested that pus from the abscess should be examined bacteriologically, as both cases ought to have a similar etiology.

$^{21}/_{5}$. Puncture of the abscess in the knee. Thick pus. — Culture: Salmonella paratyphi type C. Guinea pig test and Löwenstein culture negative. $^{25}/_{5}$. Incision. Abundant secretion for a week, and then rapid regression with simultaneously improved general condition; the patient becomes afebrile and puts on weight. $^{30}/_{5}$. Culture from faeces and urine negative.

Roentgenogram $^{1}/_{6}$: Increased destruction, now encompassing the whole upper medial part of tibia from the epiphyseal line and 3 cm downwards. A 4—5 cm long periosteal deposit on the lateral and posterior part of tibia.

$^{7}/_{6}$. Blood: Positive Widal reaction for type B paratyphoid fever H $^{1}/_{40}$ and type C paratyphoid fever H $^{1}/_{160}$.

Roentgenogram $^{11}/_{6}$: Destruction somewhat diminished; the skeletal structure appears more distinctly.

Roentgenograms $^{25}/_{6}$ and $^{11}/_{7}$ show a continued regression. $^{17}/_{8}$ 1945 the process is roentgenologically healed. The patient has now no symptoms from the leg, is in good general condition and puts on weight all right.

Case 3. A M. Born $^{22}/_{3}$ 1945.

Admitted to the Pediatrical Dept. $^{5}/_{5}$ 1945 in an emaciated state and poor general condition. Temp. 38—39°. Bronchopneumonia. Anaemia and leukocytosis.

$^{23}/_{5}$. Further deterioration with meningitis. Mantoux negative. $^{7}/_{6}$. Meningitis in subsidence, improved general condition. $^{25}/_{6}$. The patient moves his right leg badly. Swelling proximal to the knee joint. Another bout of high fever with general deterioration. Sulfatiazol treatment.

Roentgenogram $^{26}/_{6}$. Round the inferior part of the right femur there is a periosteal deposit a couple of mm thick. In the metaphysis up to the epiphyseal line the bone structure is thinned out over a band-shaped area, which continues proximally a couple of cm from the epiphyseal line. — From the similarity of the roentgenogram with those obtained in cases 1 and 2, we suspected a paratyphoid etiology.

$^{29}/_{6}$. Blood: Positive Widal reaction for type B paratyphoid fever H $^{1}/_{160}$, for type C paratyphoid fever H $^{1}/_{160}$, and for type C paratyphoid fever O $^{1}/_{160}$. $^{2}/_{7}$. The patient moves his leg easily and has no pains. The swelling persists. General condition improving. Wassermann reaction negative. $^{5}/_{7}$. Faeces: Culture yields Salmonella paratyphi type C. Urine: No growth.

$^{17}/_{8}$. Good general condition. Satisfactory increase of weight. Afebrile since the beginning of July. No symptoms from the right knee.

Roentgenogram $^{17}/_{8}$ 1945: Osteitis healed. The periostites are well circumscribed and healing.

SUMMARY

The author reports 3 cases of refugee infants with a roentgenologically demonstrated osteitis with periostitis in the metaphyses round the knee joint. All the three cases presented about the same picture, and it was possible to demonstrate bacteriologically that the paratyphoid bacillus was the etiological factor. The bone changes healed within 2—3 months in all the three cases.

ZUSAMMENFASSUNG

Verf. berichtet über 3 Fälle von Flüchtlingkindern mit röntgenologisch festgestellter Osteitis mit Periostitis in den das Kniegelenk umgebenden Metaphysen. Sämtliche drei Fälle wiesen ungefähr das gleiche Bild auf, und es liess sich bakteriologisch nachweisen, dass der Paratyphusbazillus den ätiologischen Faktor darstellte. Die Knochenveränderungen heilten in sämtlichen drei Fällen in 2—3 Monaten aus.

RÉSUMÉ

L'auteur relate le cas de 3 enfants — des réfugiés — atteints d'ostéites, démontrées par les Rayons Roentgen et accompagnées de périostite au niveau des métaphyses voisines du genou. Tous les trois présentaient à peu près la même image, et il fut possible de prouver bactériologiquement que le bacille du paratyphus en était le facteur étiologique. Les lésions osseuses guérirent en 2—3 mois dans les trois cas.

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THE ORIGIN OF ALBINA AND XANTHA MUTATIONS IN BARLEY[1]

by

Åke Gustafsson.

In 1940 the present author published an analysis concerning the origin of induced chlorophyll mutations in barley. In the material examined certain group characteristics were revealed. For instance, *xantha* types (lacking green substances) concentrated to the offspring of distinctly but slightly sterile X_1-plants. *Viridis* types (having green and yellow substances but in altered amounts) showed an even higher dependence on X_1-sterility. *Albina* mutations (lacking green and yellow substances) readily arose from normally fertile X_1-plants as well. Since high X_1-sterility is consequent upon chromosome disturbances, these results were taken to indicate a certain connection between the type of genomatic change and the type of chlorophyll mutation.

These conclusions were criticized by MÜNTZING (1942), as well as by FREISLEBEN and LEIN (1943). The experiments of these workers, however, are open to some counter-criticism. In this paper the discussion will be confined to albina and xantha mutations.

Material

For many years extensive irradiation experiments have been performed with the express purpose of inducing chlorophyll mutations in barley. The dosages applied varied in the series to be reported here from 1,000 to 25,000 *r*-units. Seeds were pre-treated in various manners. This has no influence whatsoever on the present results, since mutations behave exactly similar with regard to original X_1-fertility, whether originated from dry or pre-treated seed series. Most irradiation work was carried out at the Radiophysics Institute, Stockholm (Director: R. SIEVERT), under the supervision of Dr. A. FORSSBERG. The Roentg.-rayed seeds were sown in the field and gave rise to X_1-plants, more or less sterile owing to the dosage applied and the physiological state of the treated seeds.

[1] Submitted for publication, Dec. 31, 1945.

The number of fertile and sterile flowers per ear and plant was continually counted. Therefore we know the exact fertility of every X_1-plant in the progeny of which a chlorophyll (or other) mutation has arisen, but we also know the fertility of the non-mutated sister plants. The average fertility of untreated plants varies between 95 % and 98 %. On the basis of its decreasing fertility the material may be divided into four groups. The X_1-plants belonging to the region with 90—100 % fertility will be denoted as »normally fertile».

Table 1.

The percentage of X_1-plants in different fertility ranges.

		Fertility ranges									
	Dosages applied	0 — 10	— 20	— 30	— 40	— 50	— 60	— 70	— 80	— 90	— 100 %
Group 1.	1,000—10,000 *r* . .	—	—	—	—	0.2	0.9	3.9	11.4	26.8	56.8
» 2.	5,000—10,000 *r* . .	—	—	—	0.1	1.0	4.8	9.6	23.4	32.5	28.6
» 3.	7,500—15,000 *r* . .	—	—	0.7	1.9	3.9	9.9	21.8	26.7	22.8	12.4
» 4.	10,000—25,000 *r* . .	—	0.4	0.7	3.3	10.0	16.0	26.3	22.5	16.0	4.7

Dosages applied	N	Number of albinas	Number of xanthas
Group 1. 1,000—10,000 *r*	1,426	59	10
» 2. 5,000—10,000 *r*	830	63	11
» 3. 7,500—15,000 *r*	881	94	15
» 4. 10,000—25,000 *r*	957	97	15

Group 1: 6 series, 40—80 % normally fertile X_1-plants.
» 2: 4 » 23—36 » » » » »
» 3: 6 » 10—20 » » » » »
» 4: 10 » 0.5—9.7 » » » » »

Albina and xantha mutations in comparison

Total material.

Xantha mutations, as defined here, arose more rarely than albinas, in fact about six times as seldom. Both types increase in number when dosage increases, but there is no direct relationship, owing to secondary processes of selection (GUSTAFSSON, 1946).

With all four groups summed up, there are 1,201 X_1-plants in the range of 90—100 %. This makes 29 % of the total number. In the same range we find 22 percent of all discovered albina mutations, a reasonable agreement. Only three out of 51 xanthas occur here, *i. e.* about 6 %. The X_1-plants of these three mutations showed 91, 91 and 96 % fertility respectively, in the first two cases a slight but distinct decrease compared with the control. In the third case, in one and the same ear progeny there appeared one albina and one alboviridis mutation in addition to the xantha

type. This indicates a series of rather complex happenings in spite of the normal fertility.

The mutation distribution in the region 90—100 % as against the 10—90 % regions gives a χ^2 of 7.43 with a P-value above 0.001 but below 0.01. Apparently the conclusion from 1940 holds good, *i. e.* xantha mutations do not easily arise in the offspring of normally fertile X_1-plants.

The average fertility of 313 X_1-plants producing albinas is 78 %, that of 51 X_1-plants producing xanthas is 76 %. The difference is not significant. A further analysis explains this state of things.

The fertile plant groups (1 and 2).

Group 1 comprises six series and has more than half the X_1-plants normally fertile. In the same range 56 % of the albinas are found, a close agreement. Only 10 % xanthas occur here (the single above-mentioned case with three mutations in the same progeny). The difference in distribution is obvious. The χ^2 equals 7.85, $0.01 > P > 0.001$. The average fertility of 59 X_1-plants, giving albinas, amounts to 88.9 ± 1.1 % and that of 10 X_1-plants, giving xanthas, is 84.0 ± 1.7 %. This gives a t equal to 2.46 and $0.02 > P > 0.01$. In this group the *average* fertility also shows a rather striking type difference.

Group 2, consisting of four series, has slightly more than one fourth of the X_1-plants in the 90—100 % range. Every fourth albina type is encountered here, against no single xantha mutation. According to YATE's correction for small numbers the difference in distribution corresponds to a P-value of less than 0.2 but higher than 0.1. Highly significant, however, are the average fertilities. The X_1-plants of 63 albinas show 83.1 ± 1.2 % against 72.3 ± 2.7 % for 11 X_1-plants with xanthas. The difference gives a t equal to 3.62 and $P < 0.001$.

Groups 1 and 2 together give the following distributions:

	Obtained number of mutations				Expected number of mutations			
	0 — 80 — 90 — 100 % fertility				0 — 80 — 90 — 100 % fertility			
Albina	28	45	49	= 122	33.27	46.07	42.66	= 122.00
Xantha	11	9	1	= 21	5.73	7.93	7.34	= 21.00

$\chi^2 = 12.68$, two degrees of freedom, $0.01 > P > 0.001$.

The average fertility of 122 albina X_1-plants is 85.9 ± 0.9 %, that of 21 xantha X_1-plants is 77.9 ± 2.1 %. t amounts to 3.56 and P lies below 0.001, *i. e.* there is less than one chance in a thousand that the difference is not real.

The sterile plant groups (3 and 4).

In group 3 nineteen out of 94 albina mutations (20 %) arose in the normally fertile region, and two out of 15 xanthas (13 %), still a small

surplus of albinas. Moreover the two xanthas, as mentioned previously, arose from X_1-plants less fertile than the control, both of them showing 91 %. There still occurs a small difference between the types of mutation in average X_1-fertility, albinas having 76.8 %, xanthas 75.7 %, but it is not significant.

In group 4 hardly any normally fertile plants are found. As a consequence we meet only a few albina types here (two out of 97, *i. e.* 2 %), but also no xanthas (out of 15 cases). The average fertility of X_1-plants giving albinas is 72.5 %, that of X_1-plants giving xanthas is 72.6 %, a close agreement.

The reason for this behaviour is obvious. The highly sterile X_1-plants increase in number at the cost of normally fertile ones. Therefore most of the mutations occurring, whether albinas, viridis or xanthas, will appear in the low fertility regions. Chromosome disturbances and gene changes will mix. Differences in distribution will automatically disappear. In addition, the few »normal» plants as well will contain gross irregularities, although by chance exhibiting no signs of decreased fertility.

X_1-plants and mutations in comparison

Total material.

Another point of interest attaches to the distribution of mutations relative to the number of X_1-plants in the different fertility ranges. The following table gives the condensed data:

	Fertility of X_1-plants										
	0 — 10	— 20	— 30	— 40	— 50	— 60	— 70	— 80	— 90	— 100 %	
No. of X_1-plants . . .	—	4	13	50	141	293	580	807	1,005	1,201	= 4,094
No. of albina mutations	—	—	1	5	9	21	41	78	88	70	= 313
No. of xantha mutations	—	—	—	—	2	1	12	16	17	3	= 51

From these data the distribution of albina and xantha mutations may be computed. *First* the albinas: If mutated and non-mutated X_1-plants are compared, we find a certain surplus of mutated plants in the two regions of 70—80 and 80—90 % fertility and a corresponding deficit in the normal region 90—100 %. For five degrees of freedom (10—50 % must form one range) $\chi^2 = 12.4$ corresponds to $0.05 > P > 0.02$, *i. e.* a slight deviation from a normal distribution. *Then* the xanthas: Here the five regions of 10—60 % must be united. Mutated and non-mutated X_1-plants, when compared, give an $\chi^2 = 19.75$. With four degrees of freedom we find a P-value well below 0.001. Deficits of mutations occur in the most sterile and most fertile regions.

The contrast between the two types of mutation is evident.

The fertile plant groups (1 and 2).

The materials of groups 1 and 2, treated in the same manner as above, give the following relative distributions of mutated and non-mutated X_1-plants.

		χ^2	D. F.	P	Fertility ranges	Smallest expected number of mutations in any range
Group 1.	Albina . .	0.66	2	$0.8 > P > 0.7$	—80—90—100 %	> 9
	Xantha. .	8.99	1	$0.01 > P > 0.001$	—90—100 »	> 4
Group 2.	Albina . .	4.11	3	$0.3 > P > 0.2$	—70—80—90—100 »	> 9
	Xantha. .	9.17	2	< 0.001	—80—90—100 »	> 3
Groups 1 + 2	Albina . .	4.79	3	0.2	—70—80—90—100 %	> 10
	Xantha. .	15.92	3	< 0.001	—80—90—100 »	> 5

There is hardly any doubt that the two types of mutation behave differently. Albinas distribute at random over the whole fertility range. This is not the case with the xantha mutations, however.

The sterile plant groups (3 and 4).

Here the behaviour is quite reverse to that of groups 1 and 2. We find the following distribution data:

		χ^2	D.F.	P	Fertility ranges	Smallest expected number of mutations in any range
Group 3.	Albina	9.23	4	0.05	—60—70—80—90—100 %	> 11
	Xantha	0.19	2	0.9	—70—80—100 %	> 4
Group 4.	Albina	11.28	5	0.05	—50—60—70—80—90—100 %	> 4
	Xantha	4.20	3	$0.3 > P > 0.2$	—60—70—80—100 %	> 3
Groups 3 + 4	Albina	12.08	5	$0.05 > P > 0.02$	—50—60—70—80—90—100 %	> 15
	Xantha	4.91	3	$0.2 > P > 0.1$	—60—70—80—100 %	> 7

Evidently, when the chromosome aberrations become frequent and the X_1-sterility increases, albina mutations will be irregularly distributed. Xantha mutations on the contrary spread at random over the fertility ranges. This accords with the alleged origin of albinas as intragenic or »point» mutations. Under low X-ray effects intragenic changes and chromosomal rearrangements run largely independently. In the case of high effects they intermingle in various ways. Such mutations as albinas, which are fundamentally intragenic, will be plastered with numerous chromosome aberrations and their distribution consequently erratic. Xanthas, on the other hand, which are associated with X_1-sterility and as a consequence with chromosome aberrations, will distribute at random when the aberrations become numerous.

Discussion

From the facts presented above we may draw the following conclusions:

Albina mutations differ from the xantha types with regard to their general independence of X_1-sterility and hence of chromosome aberrations.

Albina types also arise abundantly from X_1-plants that, as indicated by their full fertility, are not hampered by structural rearrangements or gross chromosome abnormalities. Xantha mutations cannot arise from such plants. For their origin they require an obvious decrease in X_1-fertility, although this decrease need not be very great.

As a consequence, X_1-plants giving rise to albina mutations show an average fertility higher than that of X_1-plants producing xanthas. This applies to all material, but is especially evident after weak X-ray effects.

In the most fertile series (groups 1 and 2) albina types distribute at random over the whole fertility range. Xanthas do not. This is taken to indicate an average intragenic or »point» origin of albinas. Xanthas, on the contrary, arise exclusively after some crude happenings, probably after structural aberrations of some kind.

In the most sterile groups (3 and 4), where chromosome rearrangements are specially frequent, albinas distribute irregularly over the regions set forth. Xanthas, however, distribute at random.

These results suggest some sort of difference between albinas and xanthas as *types of mutation*. Of special importance is the fact that xanthas cannot arise from the offspring of normally fertile plants, at least not in the varieties examined here. So far no two albinas or xanthas in barley have been shown to be caused by identical genomatic changes, although some cases of multiple alleles are found.

What then are the causes of the conflicting results presented by MÜNTZING and by FREISLEBEN and LEIN? The former author lumped xantha, alboviridis and viridis types together, which is one source of error. Field material was exclusively used, where classification is difficult and harsh conditions (like those in the spring of 1941) decrease germination and sprouting ability, especially of embryos and seedlings which are sublethal, owing in part to cytological disturbancies. The sterility was determined in a manner different from that of the present author. Not the total plant sterility was calculated, only that of three ears per plant. Furthermore, the X_2-generation does not reveal more than one half of the induced chlorophyll mutations (GUSTAFSSON, 1946), and this under laboratory conditions. Therefore the data put forward by MÜNTZING cannot be regarded as critical, and he himself refrains from definite conclusions.

FREISLEBEN and LEIN express themselves more emphatically. They state »dass keinerlei Beziehungen zwischen bestimmten Mutationstypen

und den Fertilitätsverhältnissen bestehen» (p. 270). Their method of determining the X_1-fertility is however incorrect. In their investigation the fertility of the control runs no higher than 87 % against a real value of 95—98 %. »GUSTAFSSON hat eine genauere Methode zur Bestimmung der Fertilität angewendet, da bei unseren Bestimmungen die Fertilität der unbehandelten Serie bereits um 13 % herabgesetzt ist» (p. 251). This fact seems to undermine their own conclusion. They have induced an immense number of chlorophyll mutations and obtained many important results. But no one can study the rôle of fertility successfully without determining fertility correctly.

Nevertheless their figures rather support the conclusions arrived at here. Their data are presented in tables 8 and 9 (pp. 269 and 270). The fertility ranges are 0—20—40—60—80—100 %. The region of 80—100 % answers to the region of 90—100 % in the present paper. In table 8 we find 254 »normally fertile» X_1-plants out of 1,817, *i. e.* 14 %. Consequently this table corresponds to group 3 in my material, where sterility is pronounced and possible differences between albinas and xanthas are smoothed out. In the region 80—100 % sixteen albinas occur, equal to 12 % of the total number, a rather fair agreement with the percentage in my material and with the number of »normal» plants. None out of 12 xanthas arose here. The mutual difference in distribution is not significant but runs in the same direction as in my material.

In table 9 we find no more than 189 »normal» X_1-plants out of 3,000,[1] *i. e.* 6 %. This table therefore corresponds to group 4 in the present paper. In the same region there are thirteen albinas (5 %) and two xanthas (9 %). The difference has ceased to exist. This was to be expected, since chromosome abnormalites are potent.

Analysing table 9 further, we find that albinas distribute irregularly over the fertility ranges set up, P is much less than 0.001 (four degrees of freedom). Xanthas distribute at random, a P-value of 0.7 is obtained (two degrees of freedom). The data of the two authors, if anything, support the results presented here, at any rate they do not contradict them.

Prof. Dr. G. BONNIER, Stockholm, and Dr. O. TEDIN, Svalöf, have indicated the methods of statistical approach used in this paper.

SUMMARY

On an enlarged material it is shown that the conclusions put forward by GUSTAFSSON (1940) hold true, at least with regard to albina and xantha mutations. The material has been more profoundly analysed here. Albina mutations arise independently of X_1-sterility and chromosome disturbances. Xantha mutations cannot arise from normally fertile

[1] The total number is 2996 instead of 3000.

X_1-plants; they require special conditions that decrease fertility. The two types of mutation behave strikingly different, whether in fertile or in highly sterile series.

Objections to the previous results, raised by MÜNTZING and by FREISLEBEN and LEIN, rest upon mistakes in classification, errors due to field material or to incorrect determination of X_1-fertility. The data given by the last-mentioned two authors do not contradict, but rather support the present writer's conclusions.

ZUSAMMENFASSUNG

An einem nun grösserem Material konnte gezeigt werden, dass die von GUSTAFSSON (1940) gezogenen Schlussätze richtig waren, wenigstens hinsichtlich albina- und xantha-Mutationen. Das Material ist hier gründlicher untersucht worden. Albina-Mutationen entstehen unabhängig von X_1-Sterilität und chromosomalen Störungen. Xantha-Mutationen können nicht ihren Ursprung in normal fertilen X_1-Pflanzen haben; sie erfordern besondere Bedingungen, die die Fertilität herabsetzen. Diese zwei Typen von Mutationen verhalten sich auffallend verschieden, ob sie nun in fertilen oder in hoch sterilen Serien vorkommen.

Einwände gegen die früheren Ergebnisse, die von MÜNTZING und von FREISLEBEN und LEIN erhoben worden sind, beruhen auf Klassifikationsfehlern, Irrtümern in bezug auf das Feldmaterial oder auf unrichtiger Bestimmung der X_1-Fertilität. Die von den beiden letztgenannten Verfassern gemachten Angaben widersprechen nicht sondern eher stützen die Schlussätze, die vom Verfasser der vorliegenden Arbeit gezogen worden sind.

RÉSUMÉ

Sur un matériel agrandi l'auteur donne la preuve, que les conclusions, faites par lui (GUSTAFSSON 1940), sont valables, au moins en ce qui concerne les mutations albina et xantha. Le matériel a été cette fois analysé plus profondément. Les mutations albina apparaissent indépendemment de la stérilité X_1 et des perturbations chromosomiques. Des mutations xantha ne peuvent pas sortir des plants X_1, normalement fertiles; elles exigent des conditions spéciales, qui diminuent la fertilité. Les deux types de mutations restent strictement différents, autant dans les séries fertiles que dans les séries largement stériles.

Des objections contre les résultats antérieurs, faites par MÜNTZING et par FREISLEBEN et LEIN, ont été provoqués par des erreurs de classification, erreurs dues au matériel de culture en plein air ou à la détermination incorrecte de la fertilité X_1. Les indications, donnés par ces deux derniers auteurs, ne contredisent pas les conclusions de l'auteur en question, par contre elles les confirment.

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FROM THE RADIOPHYSICAL INSTITUTE OF KING GUSTAF V'S JUBILEE CLINIC, STOCKHOLM
(CHIEF: PROF. R. SIEVERT)

THE CONNEXION BETWEEN ROENTGEN RAY RISKS FOR WORKERS AND CHANGES IN THEIR BLOOD PICTURES[1]

by

Matts Helde

Introduction

A great number of authors point out that in radiological work severe injuries to the blood often do not appear until a very long time, after 15—20 years or more, and then often very rapidly change for the worse. Long before that, however, premonitory changes in the blood picture should be observable. So far, the attempts made to ascertain what these premonitory changes are, are as a rule founded either on experience from patients undergoing roentgen treatment or on a comparatively small material. To be on the safe side we might say that rather little is known of the influence of very small doses or intensities on the normal blood picture. This has also been pointed out by various authors.

The Swedish Roentgen Ray Protection Law of 1941 aims at preventing injuries to patients, to roentgen personnel and other persons living in the risk zone of the roentgen establishment, *e.g.* people in the neighbourhood. One link in the supervisional work provided for in the law is repeated inspections of the establishment, equipment and conditions of work, coupled with annual investigations of the blood pictures of the staff, partly in order to avoid physically determinable obviously bad conditions, which with some reason may be called obnoxious, and partly in order to check the efficacy of these inspections and investigations by the determination of any subsequent changes in the blood picture and so ward off in time any incipient dangers. Some of the factors taken into consideration in surveying an establishment are: the competence of the leader of the radiological work, the technical standard of the equipment in use (roentgen ray set with the requisite auxiliary apparatus), its aptness for the

[1] Submitted for publication, Febr. 15, 1946.

work, and the special local technique (owing to special investigations, working speed, or special clientele, *e.g.* children, old people, or lunatics). Local conditions, such as the existence of satisfactorily protected operators rooms, the possibility of using their facilities, adequacy of laboratories, the disposition of the available space (placing of furniture, roentgen ray insulation from adjacent rooms and the use of these) must also be taken into consideration in surveying the establishment. The factors here exemplified are so interwoven, that an absolutely objective classification of an establishment according to its riskiness to the staff is impossible. Attempts at such a classification by direct measurements of doses on working personnel have been made, but they have not given good results, probably because the working staff will take greater care, when they know that they are observed.

In drawing directions for improving the roentgen ray protection survey it is of course very important to verify by some means the value of the present views on this subject. Here we examine changes in the blood pictures of the staff working under conditions of different riskiness. But since the attribution of an establishment to a certain class of risks — although some extant subjectiveness in the estimation — cannot entirely lack a corresponding basis of reality, comparisons between given risk-classes and the blood pictures of their staffs should also provide information on the suitability of the different changes in the blood picture as indicators of bad conditions in given premises. Before such an investigation can be undertaken, however, premises must be classified according to their riskiness, and the staff into groups with a view to blood picture.

Methods of investigation

From the *radiophysical point of view* premises should first be classified according to their expected riskiness. This classification is based on reports from surveys of existing premises, and completed by drawings, actual voltage and dose measurements, and by any other available information of any importance to the classification. In order to obtain the greatest possible uniformity, this classification was made by two men with great experience of surveys of this kind (industrial and diagnostic radiology), who both surveyed more than 2,000 establishments — some hundreds of them repeatedly — keeping in constant touch to verify their respective experiences. Estimated tables on radiophysical or other empirical bases were employed as far as possible in calculating risk of exposure indices. The following table may be given as an example of this.

A compound risk-index including only these two factors is obtained by multiplying the two corresponding indices; other factors are included by further multiplication by their risk-indices. Tables as the left columns

Nr of negatives taken per week + aggregate duration, in minutes, of screenings in the same period	Risk factor	Distance from the source of the secondary radiation	Risk factor
— 5	1	10 — 7	1
5— 10	2	7 — 5	2
10— 20	4	5 — 3.5	5
20— 40	8	3.5 — 2.5	10
40— 80	16	2.5 — 2	20
80—160	30	2 — 1.5	40
160—320	60	1.5 — 1	80
a. s. o.		< 1	200

must be altered in apparently uniform work; as the right columns, when a comparatively small-sized room necessitates consideration of the levelling effect of radiations of tertiary and higher orders. In order to eliminate the subjective factor as far as possible, the observers always followed the reports of previous surveys on the originally laid down lines, without any consultation or knowledge of which establishment was concerned or — accordingly — the results of the medical examination of the staff. The resultant risk indices were divided into six groups, in which the average of each was double the average of the preceding. In order to give an idea of the closeness of the opinions of the observers as regards the risk of undesired roentgen ray exposure, we may say that in all but two of 280 establishments they arrived at the same or contiguous riskgroups. *73* % of these establishments were moreover put in the same risk class by both observers.

As this classification made the number of persons in certain classes smaller than was statistically desirable, a reclassification to a four-degree scale was undertaken. In the following these classes are designated I—IV with increasing risk of exposure. In order to smooth the subjective opinions of the observators the average of any differing estimates were used in this final scale.

As to the relation between these risk-classes and the tolerance dose recommended by the International Protection Commission of the Fifth International Congress of Radiology, it may be said that this dose quite certainly has never been exceeded in the first risk-class.

The *medical examinations* are based a) on reports on the blood pictures of the staff rendered by the several establishments, and b) on preparations sent in from various places and examined at the Radiophysical Institute. The latter group differs from the former qualitatively — apart, of course, from being uniformly examined — by the observations' also comprising the presence or not of hypersegmented leucocytes and pathologic lymphocytes, and quantitatively by having been made on only about 30 per cent of the staff suspected to this investigation.

Two classes only have been introduced: those with normal and those with abnormal blood pictures. As abnormal are here denoted blood pictures of any of the following types:

Blood constituent	Limit	Diagram number	and called there
Erythrocytes { in men	$\leq$ 4.0 mill.	1	Anemia
Erythrocytes { in women ...	$\leq$ 3.5 »	1	Anemia
Hemoglobin { in men	$<$ 80 %	1	Anemia
Hemoglobin { in women ...	$<$ 75 »	1	Anemia
Leucocytes	$<$ 4 000	1	Leucocytopenia
»	$>$ 10 000	4	Leucocytosis
rod forms	$>$ 5 %	2	Shift to the left
basophil cells...	$>$ 1 »	4	Basophilia
lymphocytes ...	$>$ 45 »	2	Granulocytopenia
»	$<$ 17 »	2	Granulocytosis
Morphologic changes:			
Hypersegmented leucocytes	—	3	Hypersegmentation
Pathologically changed lymphocytes	—	3	Pathologic lymphocytes

[1] Only those with index less than 0.9 are included.

The material examined

The material which has thus been classified radiophysically and medically comprises — as we have said before — the staff employed in radiological work (medical, veterinary, odontological and industrial). The analysed material refers to 1,406 persons at 280 different establishments, the number of persons in each of the four risk classes varying from 72 to 820. During the work, however, it was found that a further analysis of 716 persons from 240 establishments, included in the former material, was motivated. In this analysis the number of persons in each of the four risk classes varied from 67 to 293.

One reason for this partition was that establishments returning a large number of persons examined seem to have reported blood investigations of persons who apparently had nothing to do with the actual roentgen work. This might be due to a misunderstanding of the directions for performing the investigation. Establishments sending in returns for a smaller staff, on the other hand, are more likely to have themselves sifted the material rationally. In order to avoid any subjective opinions a border line between the two categories of establishments was fixed arbitrarily, and the number selected was 10.

If a »partial» investigation gives results congruent with those obtained from the whole material, any conclusions drawn will rest on a firmer foundation. For reasons mentioned above the results obtained from the

partial material from establishments with less than 10 blood reports sent in must be considered to offer the surest premises for drawing conclusions. The fact that the partial material generally comes from smaller establishments also contributes to this, as this permits a better survey of the working conditions at these places when inspected, resulting in a better estimate of the radiophysical conditions.

The interpretation of the *morphological changes* (1) in the blood pictures is, however, based upon a smaller material than that mentioned above, as it includes only cases remitted to the institute.

The whole material consists in this case of 401 persons, varying from 9 to 254 in each risk class. The partial material (from the smaller establishments) relating to morphological changes consists of 180 persons in all, varying from 9 to 85 in each risk class.

The results are shown in the diagrams 1—4.

The diagrams, and a discussion

In the diagrams the risk of classes are marked on the abscissa and the percentile proportions of persons with »abnormal» blood picture in each class on the ordinate. The ordinates can thus be said to express the risk in the several classes of the roentgen work producing abnormal blood pictures.

If the diagrams are tested by the standard error, we find that the ordinates corresponding to class I and II respectively may be displaced — either disturbing or promoting the monotone of the diagram — in the anemia and leucocytopenia diagrams obtained from the partial material and in the anemia, leucocytopenia and leucocytosis diagrams obtained from the whole material. In class III and IV corresponding displacements of the ordinates may occur in cases of basophilia and leucocytosis in the partial material and cases of basophilia, shift to the left, leucocytosis, granulocytosis and pathologic lymphocytes in the whole material. Of course there is no certainty of securing a monotone diagram if the ordinates in neighbouring classes are equal or nearly equal, as they are in the partial material in respect of granulocytopenia in classes II—III and in both the whole and the partial material in respect of basophilia in classes I—II.

The significance of the material has been controlled by comparison with normal material from persons who have done no roentgen work and was then found to fulfil satisfactorily the »three times the standard error» demand, except in some cases of class I (which of course is not surprising considering the fact that this class includes the establishments of the highest standard) and — in two of the classes — in cases of leucocytosis.

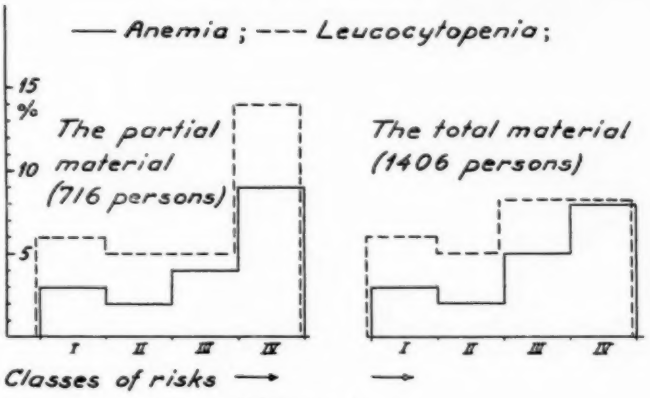

Diagram 1

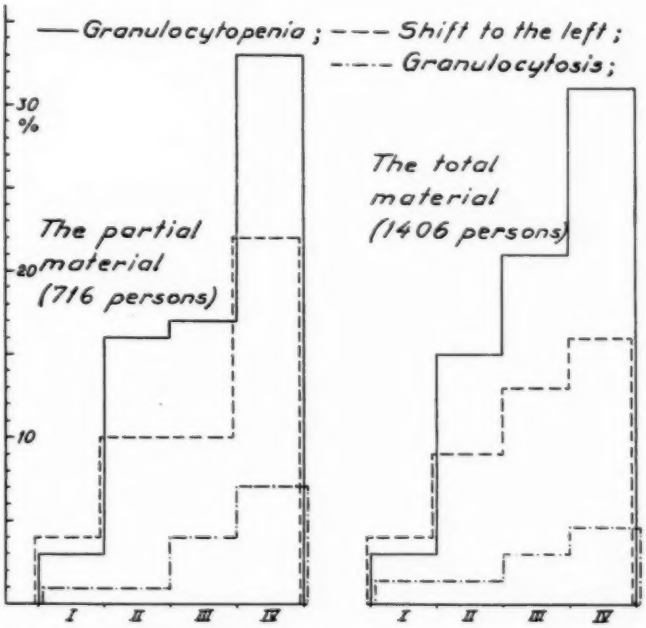

Diagram 2

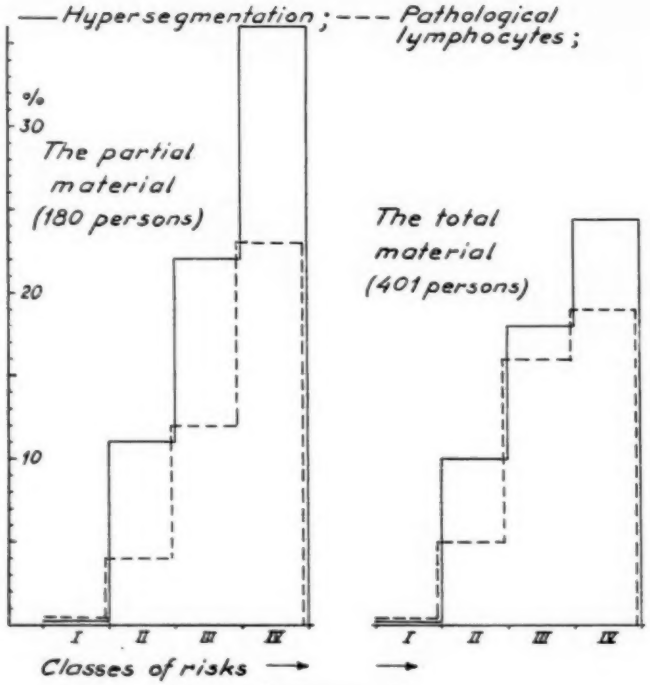

Diagram 3

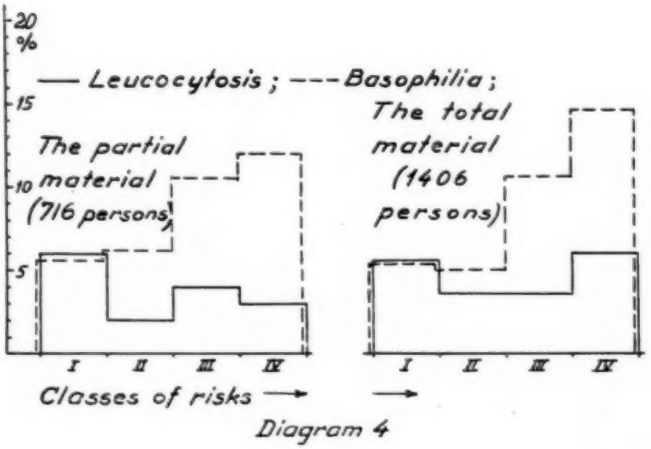

Diagram 4

These investigations, and the congruence of both the whole and the partial material diagrams (the difference occurring was expected!) justify an emphasizing that the blood changes here interpreted (except as regards leucocytosis) are well suited to indicate bad conditions in a roentgen establishment. The steeper the slope of the diagram with increasing riskiness of the work, the more suitable is this type of change in the blood picture for pointing out faults. Naturally, no conclusions about an establishment can be drawn from a single anomaly, possibly after repeated examinations; but conclusions can be drawn if several anomalies are combined in one blood picture, or when changes in the picture have been observed in several persons at the same establishment.

The diagrams show that hypersegmentation, granulocytopenia, pathologic lymphocytes and shift to the left are most suitable as indicators of bad conditions at roentgen establishments. Anemia and leucocytopenia hitherto mostly used as indicators are injuries rather than premonitory changes. Accordingly they are not so frequently observed.

This paper is a preliminary report of an interpretation of the facts ascertained, and will be continued with their practical bearing upon the protective problem in roentgen work, which has not been dealt with here. All that now may be said is that too little regard seems to be paid to the riskiness of scattered radiation and that protection for this is consequently more or less neglected.

SUMMARY

The paper is a report on investigations of the connexion between risks in radiological work and several types of changes in blood pictures of the staff. Hypersegmentation, granulocytopenia, pathologic lymphocytes and shift to the left in the blood pictures of the staff seem to be the best indicators of constructional and other deficiences at an establishment.

ZUSAMMENFASSUNG

Der Aufsatz berichtet über die Beziehungen zwischen Bestrahlungsrisiko für das mit Röntgenarbeit beschäftigte Personal und verschiedenen Typen von Veränderungen im Blutbilde desselben. Hypersegmentation, Granulopenie, pathologische Lymphozyten und Linksverschiebung scheinen die sichersten Indikatoren dafür abzugeben, dass inbezug auf den Strahlenschutz durch die Anlage oder die Arbeitsweise bedingte Mängel verschiedener Art vorliegen.

RÉSUMÉ

Ce travail relate les recherches sur les rapports existant entre les risques inhérents au travail radiologique et divers types d'altérations de l'image sanguine chez les employés. L'hypersegmentation, la granulopénie, les lymphocytes pathologiques et la déviation vers la gauche, dans le sang du personnel, semblent être les meilleurs indicateurs de défauts de construction ou autres dans l'établissement.

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THE EFFECT OF ROENTGEN RAYS AND ULTRA-VIOLET RADIATION ON THE PERMEABILITY OF YEAST[1]

by

G. Hevesy and *K. Zerahn*

It was repeatedly discussed that the effect of roentgen rays on animal and plant tissues may be partly or wholly due to a changed permeability of the cells. A change in the permeability of tissue cells may influence the rate of influx of substances into the cell participating in synthetic processes which ultimately lead to cell division; it may moreover affect the rate of efflux of vast products from the cell. It is, however, very improbable that the main effect of roentgen rays on cell division should be primarily due to a change in permeability, as much evidence gathered in recent years indicates that the effect of roentgen rays on cell division is due to the blocking of fundamental reactions as, for example, the formation of desoxyribose nucleic acid, going on in the nucleus. It is conceivable, on the other hand, that the effect of roentgen rays on cell division is due partly to an effect of the radiation on the cell permeability.

With the aim to investigate the possible existence of such an effect we compared the permeability of yeast cells both to phosphate and to potassium, before and after irradiation, using ^{32}P and ^{42}K, respectively, as indicators.

Yeast cells are very resistant to the effect of roentgen rays, which makes them well suited for such investigations. Large doses necessary to kill yeast cells can earlier be expected to affect the cell permeability than small doses. Yeast cells are several hit-systems, *i. e.* they claim several hits before a lethal effect is obtained. Such systems are killed more effectively by soft than by hard radiation in view of the higher density of ionization produced by the former. While half of the yeast cells was found by v. EULER, AHLSTRÖM and HÖGBERG (1) to be killed by 30,000 r, when 180 kV roentgen rays were applied, the corresponding value found by us when applying a therapy tube operated with 60 kV was 19,000 r.

[1] Submitted for publication, Febr. 13, 1946.

RUNNSTRÖM et al. (7), who investigated the effect of roentgen rays on the fermentation of dry baker's yeast, could not observe any effect even when administering a dose of 120,000 r.

It is not advisable to carry out such permeability investigations by determining the amount of phosphate or potassium penetrating into the yeast cells before and after irradiation. The growth of the yeast claims the influx of substances required by growing cells; obstruction of the growth by irradiation, however, diminishes the influx of such substances. This diminution should not necessarily be interpreted as a consequence of altered permeability of the yeast cells; it can be and is presumably due to other factors than changes in the structure of the phase boundary. This argument does no longer hold when the following procedure is chosen. The yeast is grown in the presence of labelled phosphate and labelled potassium, respectively, and correspondingly all or almost all phosphorus or potassium present in the yeast cells is labelled. The labelled yeast is then shaken with non-radioactive nutrient solution, and the amount of ^{32}P and ^{42}K, respectively, migrating from the cells into the nutrient solution, is determined. Simultaneously, experiments are performed in which the yeast cells are irradiated previous to shaking them with inactive nutrient solution. If no difference is found in the amount of ^{32}P and ^{42}K, respectively, immigrating from the cells, we have to conclude that the irradiation has no effect on the permeability of the yeast cells.

Experimental Procedure

The yeast (Saccharomyces cerevisiae) used in our experiments has been grown for 3 to 5 days in beerwort at 25° C. A pure yeast culture was applied. The yeast was separated by centrifuging and was purified by repeatedly suspending it in water and centrifuging the suspension. The suspension finally obtained contained yeast corresponding to a dry substance weight of about 1.5 g. per 100 ml.

The nutrient solution (pH = 4.5) had the following composition: 1.4 g. $MgSO_4 \cdot 7\ H_2O$; 2.0 g. NaH_2PO_4; 1.0 g. KCl; 0.8 g. $CaCl_2 \cdot 6\ H_2O$; 1.2 g. $(NH_4)_2SO_4$; 0.01 g. $FeCl_3 \cdot 6\ H_2O$; 100 g. saccharose; 0.2 γ biotin; 100 γ aneurin; 2 mg. β-alanin; 2.0 g. citric acid per liter. The Na_2HPO_4 and the KCl, respectively, were replaced by labelled Na_2HPO_4 and labelled KCl, respectively, in those cases in which the permeability of the yeast cells was investigated.

At the start of the experiment, 1 volume yeast suspension was mixed with 1 volume nutrient solution. The dry substance of the yeast was determined in the usual way by filtering the suspension through a glass filter (1 G 4 Schott) and by drying the yeast at 105° C. The radioactivity

of ^{32}P was determined by precipitating the free phosphate, the ashed total acid-soluble fraction or the total P of the ashed sample to be investigated as ammoniummagnesium phosphate. The radioactivity of ^{42}K was determined after adding to the filtrate or to the extract of yeast cells obtained after extraction with trichloroacetic acid common KCl. The potassium was then precipitated as potassiumcobaltic hexanitrite.

Amount of Free ^{32}P Penetrating from the Cells into the Nutrient Solution

Yeast containing labelled phosphorus was repeatedly washed with inactive nutrient solution containing 1 g. K_2HPO_4 per liter; then it was shaken at 20° C. with inactive nutrient solution for 1 hour to 3 days. The activity of the nutrient solution was determined and compared with the activity of the cells. One ml. yeast suspension on the average contained 8 mg. of dry cell substance. Some of the results obtained are shown in Table 1.

As shown in Tables 1 to 6, about 1 to 2 per cent of the total ^{32}P content of the cells migrates only daily into the nutrient solution as free ^{32}P. The actual loss of free ^{32}P by living cells is presumably still lower than the above figure, as some autolysis of the cells takes place during the experiment and part of the ^{32}P present in the nutrient solution may originate from such autolyzed cells. It was already earlier found (2) that the phosphorus atoms present in the yeast cells interchange very slowly with the phosphorus atoms present in the solution in which they are suspended, and BRANDT (3) has found that in the course of 2 hours baker's yeast suspended in a succinate buffer loses 0.2 to 0.3 per cent of its phosphorus content at 25° C.

Effect of Roentgen Rays on the ^{32}P Permeability

When testing the effect of roentgenrays on the phosphorus interchange, we placed 1 ml. yeast suspension in a glass tube of 8 mm. diameter; the tube was irradiated with a non-filtered 60 kV radiation emitted by a copper anticathode for 30 minutes, the total dose administered being about 30,000 r.

The comparison of the percentage of surviving cells in the irradiated samples with the corresponding number in control preparations kept under strictly identical conditions led to the result that under the action of the radiation all but 10 per cent of the cells were killed. Both the irradiated and the non-irradiated cells were washed 4 times with inactive nutrient solution; subsequently, the washed cells were shaken for 1 to 2

days with inactive nutrient solution at 20° C. 1 ml. suspension contained 8 to 10 mg. of dry yeast. The results obtained are shown in Table 1.

Table 1.

Percentage free ^{32}P migrating from cells irradiated with roentgen rays and from non-irradiated cells into the nutrient solution.

Sample	Time of experiment in days	Percentage free ^{32}P migrated
Control	1	1.8
Irradiated	1	1.2
Control	2	2.7
Irradiated	2	1.7
Control	1	1.3
Irradiated	1	0.9
Control	2	1.7
Irradiated	2	1.1
Control	1	1.7
Irradiated	1	0.8
Control	2	2.1
Irradiated	2	1.2

As seen in Table 1, a very substantial dose which kills most of the yeast cells influences the permeability to a minor extent, only, the amount of free ^{32}P migrating through the phase boundary cell/nutrient solution in irradiated yeast being somewhat less (2/3) than in the controls.

A similar result was obtained when investigating the phosphate permeability of the JENSEN sarcoma cell (8). A dosis of a few thousand r units or less, which was found to block the formation of labelled nucleic acid molecules, did not influence to any significant rate the interchange of the plasma phosphate and the phosphate of the sarcoma cells.

The Effect of Ultraviolet Radiation on the ^{32}P Permeability

Very divergent results were obtained when irradiating yeast cells with ultraviolet radiation. In these experiments, a mercury discharge lamp (type Osram Hg Q 500) was used, which irradiated a quartz vessel containing 25 cc. yeast suspension. The distance of the vessel from the lamp was 25 cm. The results of such experiments are recorded in Table 2.

In experiments b) a very substantial increase in the amount of free ^{32}P migrating from the cells took place after irradiation. The enhanced passage of free ^{32}P from the cells into the nutrient solution can possibly be explained by an increase in the intracellular free phosphate content of the cells following irradiation or by an increased permeability of the phase boundary. With the aim to test this point we determined the free phos-

Table 2.

Percentage free ^{32}P migrating from cells irradiated with ultraviolet light and from non-irradiated cells into the nutrient solution.

Sample	Time of experiment in days	Percentage ^{32}P free migrated	Ratio of ^{32}P migrated from irradiated and non-irradiated cells
a			
Control	1	1.8	2.3
Irradiated	1	4.1	
Contol	2	2.7	1.8
Irradiated	2	4.8	
b			
Control	1	1.7	6.9
Irradiated	1	11.7	
Control	2	2.1	7.3
Irradiated	2	15.3	

Table 3.

Effect of ultraviolet radiation on the free and acid-soluble P content of yeast cells.

Treatment	Fraction	Time in hours	Percentage ^{32}P content
Non-irradiated	Total P	24	100
Irradiated	Total P	24	97.3
Non-irradiated	Free P	24	29.6
Irradiated	Free P	24	27.4
Non-irradiated	Free P	24	29.7
Irradiated	Free P	24	27.7
Non-irradiated	Acid-soluble P	24	43.9
Irradiated	Acid-soluble P	24	41.9
Non-irradiated	Residual P	24	49.4
Irradiated	Residual P	24	48.1
^{32}P immigrated into the nutrient solution containing no phosphorus			
Non-irradiated	Free P	24	2.86
Irradiated	Free P	24	5.55
Non-irradiated	Total P	27	6.84
Irradiated	Total P	27	12.9
^{32}P immigrated into the nutrient solution containing 1.5 milliM phosphorus			
Non-irradiated	Free P	26	3.22
Irradiated	Free P	26	6.06
Non-irradiated	Total P	26	6.60
Irradiated	Total P	26	12.3

Table 4.

Effect of ultraviolet radiation on the free and acid-soluble P content of yeast cells.

Treatment	Fraction	Time in hours	Percentage ^{32}P content
Non-irradiated	Total P	1	100
Irradiated	Total P	1	100
Non-irradiated	Free P	1	29.1
Irradiated	Free P	1	31.1
Non-irradiated	Acid-soluble P	1	47.2
Irradiated	Acid-soluble P	1	47.1
Non-irradiated	Residual P	1	50.7
Non-irradiated	Total P	24	100
Irradiated	Total P	24	99.4
Non-irradiated	Free P	24	26.4
Irradiated	Free P	24	22.6
Non-irradiated	Acid-soluble P	24	44.6
Irradiated	Acid-soluble P	24	41.7
Irradiated	Residual P	24	50.0
	^{32}P immigrated into the nutrient solution containing 1.5 mM phosphorus		
Non-irradiated	Free P	1	0.31
Irradiated	Free P	1	0.33
Non-irradiated	Free P	24	1.25
Irradiated	Free P	24	1.50
Non-irradiated	Free P	48	2.74
Irradiated	Free P	48	3.46

Percentage survival after irradiation = 16.

phate content of the yeast cells before and after irradiation. Furthermore, we extended our studies to the determination of the immigration of the organic P from the cells into the nutrient solution.

As shown in Tables 3 and 4, irradiation does not increase the free phosphate content of the yeast cells. The increased immigration of free phosphate into the nutrient solution following irradiation must therefore be ascribed to an increased permeability of the phase boundary. This follows also from the fact, illustrated by Tables 3 to 7, that appreciable amounts of organic acid-soluble P accumulate in the suspension solution demonstrating the decreasing ability of the yeast cells with increasing irradiation to keep these substances within the cells.

In the experiments recorded in Tables 5 and 6 after irradiation with a dose of ultraviolet radiation which kills only half the cells, 2.45 per cent of the free ^{32}P and 6.3 per cent of the total acid-soluble ^{32}P of the cells was found to immigrate in the course of 24 hours, while in the con-

Table 5.

Amount of acid-soluble ^{32}P migrating in the course of 24 hours from the cells into the nutrient solution containing no phosphorus.

Treatment	Percentage surviving cells	Percentage ^{32}P content of cells	Percentage free ^{32}P migrated into the solution (A)	Percentage acid-soluble ^{32}P migrated into the solution (B)	$\frac{B-A}{A}$
Non-irradiated	100	100	1.45	4.36	2.0
Irradiated for 5 min. . .	50	98.2	2.45	6.3	1.6
10 min. . .	25	95.0	3.55	9.2	1.6
15 min. . .	5	91.0	5.0	12.0	1.4
30 min. . .	0	85.0	9.8	21.5	1.2

Table 6.

Amount of acid-soluble P migrating from the yeast cells into the nutrient solution in the course of 24 hours.

Treatment	Fraction	Percentage ^{32}P migrated into the solution
Non-irradiated	Free P	1.75
Irradiated for 5 min. . . .	Free P	2.54
10 min. . . .	Free P	3.88
15 min. . . .	Free P	7.74
30 min. . . .	Free P	11.7
Non-irradiated	Acid-soluble P	4.10
Irradiated for 5 min. . . .	Acid-soluble P	5.60
10 min. . . .	Acid-soluble P	8.44
15 min. . . .	Acid-soluble P	16.8
30 min. . . .	Acid-soluble P	24.5
^{31}P content of yeast cell		
Non-irradiated	Free P	23.5
Irradiated for 30 min. . . .	Free P	18.3
Non-irradiated	Acid-soluble P	40.8
Irradiated for 30 min. . . .	Acid-soluble P	28.0

Percentage survival after 5 min. irradiation = 59;
after 10 min. irradiation = 8;
after 15 min. irradiation = 0.

trols these figures are 1.45 and 4.36 per cent only. The ratio of immigrated acid-soluble organic ^{32}P and inorganic ^{32}P is 1.5.

Substantial amounts of both inorganic and organic acid-soluble ^{32}P are thus found in the suspension solution after shaking strongly irradiated cells for 24 hours.

Table 7.

Amount of acid-soluble ^{32}P migrating from the cells into the nutrient solution containing 0 and 1.5 mM phosphorus, respectively, in the course of 24 hours.

Treatment	^{32}P content of nutrient solution	Free ^{32}P migrated into the solution	Acid-soluble ^{32}P migrated into the solution
Non-irradiated . . .	0	2.0	5.4
Irradiated	0	3.4	8.8
Non-irradiated . . .	1.5 milliM	2.6	6.1
Irradiated	1.5 milliM	3.2	7.6

Percentage surviving cells after irradiation = 28.
1 ml yeast suspension contains 18 mg. dry yeast.

A remarkable increase in the immigrating free and organic acid-soluble ^{32}P is also shown in Table 3 and 6. In the experiment recorded in Table 4 the effect of irradiation on the permeability is less pronounced.

The presence of free ^{32}P in the suspension solution does not necessarily indicate a loss of free phosphate from the cells, since an equivalent amount of non-labelled phosphate ions of the solution may have penetrated into the cells. Such a conclusion is, however, not compatible with the fact that about the same percentage of free ^{32}P migrates in a phosphate-containing solution as in a phosphate-free solution (cf. Table 7).

Yeast cells 40 per cent of which only survived after irradiation were found by DAVIDSON (6) to give off nitrogen containing material. Furthermore, LOOFBOUROW (4, 5) found that sublethal ultraviolet irradiation, which produced negligible cytolysis, caused a marked increase in the permeability of the damaged cells. As a result of increased permeability, the grossly intact, damaged cells released appreciable amounts of growth stimulating substances and nucleotides. It is of immediate interest to note that this author found undamaged yeast cells also to release growth stimulating substances, though to a minor extent. Somewhat more than 1/5 of the effect obtained from injured cell suspension fluids was obtained by normal cell suspension fluids from yeast suspensions (*S. cerevisiae* F. B. Strain, 100 g. per liter in distilled water). The growth stimulating effect of the suspension fluid from non-irradiated cells was interpreted (10) as due to the fact that considerable cell death (about 7 per cent) necessarily occurred in the non-irradiated suspension as a consequence of the prolonged (8 hours) extraction in distilled water.

The greatly deviating behaviour shown by the cells irradiated with roentgen rays from those irradiated with ultraviolet light may be attributed to two different reasons. A very much larger energy is necessary to obtain a lethal effect when irradiating yeast with ultraviolet radiation than when irradiating with roentgen rays. While applying a roentgen

radiation of 1.5 Å wavelength, $0.8 \cdot 10^{-6}$ ergs have to be dissipated per cubic micron to obtain a reduction of 50 per cent in the living yeast cells. When applying ultraviolet light of 2,537 micron, $175 \cdot 10^{-6}$ ergs are needed to yield the same effect. Beside the much greater energy used in the experiments with ultraviolet rays, the fact that ultraviolet radiation is absorbed selectively by some of the cell constituents may be of significance in producing an enhanced permeability of the phase boundary of the yeast cells.

In one experiment the phosphate of the nutrient solution was replaced by 50 milliM. neutralized sodium arsenate per liter when shaking the active yeast cells with an inactive nutrient solution. This replacement resulted in the decrease of the immigrating free ^{32}P to half its normal value.

Effect of Irradiation with Roentgen Rays on the Permeability of Yeast Cells to Potassium

The interchange of potassium between yeast cells and nutrient solution was investigated by NIELSEN and one of the writers (9). A much larger rate of interchange was found to take place with potassium than in the case of phosphorus.

When investigating the effect of roentgen rays on the potassium permeability yeast containing labelled potassium was shaken at room temperature with a nutrient solution containing 0.15 mol. KCl. A part of the yeast was irradiated with roentgen rays previous to this treatment, as decribed on p. 317. The results obtained in these experiments are shown in Table 8.

Table 8.

Percentage ^{42}K migrating from cells irradiated with X-rays and from non-irradiated cells into the nutrient solution.

Sample	Time of experiment in hours	Percentage ^{42}K migrated	Ratio of ^{42}K migrated from irradiated and non-irradiated cells
Control	2	8	1.3
Irradiated	2	10	
Control	2	11.8	1.2
Irradiated	2	13.8	
Control	4	22	1.4
Irradiated	4	30	

The irradiation with the very substantial dose of 30,000 r necessary to kill all but 10 per cent of the yeast cells influences thus the permeability of the cells to a small extent only, the permeability of the irradiated cells being 30 per cent higher than that of the non-irradiated cells.

While in the case of phosphorus a minor decrease in the permeability after roentgen irradiation with a lethal dose was observed, in the case of potassium such a dose was found to increase the permeability of the cells to a minor extent.

Effect of Ultraviolet Radiation on the Potassium Permeability

In contradistinction to roentgen rays an only partly lethal dosis of ultraviolet radiation st ongly influences in most cases the permeability of the yeast cells to phosphate; no such effect of ultraviolet radiation was,

Table 9.

Effect of ultraviolet radiation on the amount of ^{42}K given off by the yeast cells to the inactive nutrient solution.

Treatment	Time in hours	Percentage ^{42}K loss by the cells	Ratio of ^{42}K loss irradiated / non-irradiated
Non-irradiated	1/4	7.5	1.25
Irradiated	1/4	9.4	
Non-irradiated	2	19.1	0.99
Irradiated	2	19.0	
Non-irradiated	4	39.0	1.00
Irradiated	4	39.0	

Table 10.

Effect of ultraviolet radiation on the amount of ^{42}K given off by the yeast cells to the inactive nutrient solution.

Treatment	Time in hours	Percentage ^{42}K loss by the cells	Ratio of ^{42}K loss irradiated / non-irradiated
Non-irradiated	2	18.7	1.07
Irradiated	2	20.0	
Non-irradiated	2	20.0	1.39
Irradiated	2	27.8	
Non-irradiated	2	21.6	1.68
Irradiated	2	36.4	
Non-irradiated	4	32.2	1.61
Irradiated	4	51.9	
Non-irradiated	2	7.48	1.34
Irradiated	2	10.0	
Non-irradiated	4	13.5	1.07
Irradiated	4	14.4	
Non-irradiated	2	22.8	0.93
Irradiated	2	21.2	
Non-irradiated	4	42.0	0.96
Irradiated	4	40.2	

Table 11.

Effect of ultraviolet radiation and of addition of sodium arsenate to the nutrient solution the loss of ^{42}K from the yeast cells.

Treatment	Time in hours	Percentage ^{42}K loss by the cells	Ratio of ^{42}K loss: irradiated / non-irradiated	Ratio of ^{42}K loss: presence of As / absence of As
Non-irradiated	2	22.5		
» + As	2	13.5	0.94	0.60
Irradiated	2	21.2		
Non-irradiated	4	42.0		
» + As	4	18.4	0.96	0.44
Irradiated	4	40.2		

Survival percentage = 41.

however, found on the potassium permeability of yeast, as it becomes clear from Table 8 to 10. When interpreting this result, two points have to be taken into consideration. a) The rate of immigration of ^{42}K into the suspension fluid is very much larger than the corresponding value for ^{32}P. b) In view of the rapid rate of immigration the duration of the experiments with ^{42}K is appreciably shorter than the duration of the experiments with ^{32}P. The effect of the ultraviolet radiation on yeast permeability may possibly be effective after the lapse of a day only. When carrying out experiments at lower temperature it should presumably be possible to reduce the rate of immigration of ^{42}K and correspondingly to compare the permeability of irradiated and non-irradiated yeast cells in experiments lasting 1 day or more.

Conclusions

Yeast was grown in a nutrient solution containing labelled phosphate and labelled potassium, respectively. The yeast cells were shaken with a nutrient solution and the amount of radio-phosphorus and radio-potassium, respectively, migrating from the cells into the solution was determined. Simultaneously, the behaviour of irradiated and of non-irradiated cells was investigated.

Irradiation with a dose of 30,000 r sufficient to kill all but 10 per cent of the yeast cells influences the amount of free radio-phosphorus and radio-potassium, respectively, migrating from the cells into the solution and thus the cell permeability to a very restricted extent only.

Only partly lethal doses of ultraviolet radiation were found to increase substantially the amount of free ^{32}P and organic acid-soluble ^{32}P migrating from the cells into the nutrient solution, not however the rate of migration of ^{42}K.

Irradiation does not increase the free phosphate content of Hast cells. The phase boundary is thus influenced by the effect of the radiation.

The migration of intra-cellular ^{32}P into the nutrient solution is not an interchange process, as the same percentage of ^{32}P migrates into a phosphate-containing as into a phosphate-free solution.

When the yeast cells were shaken with a nutrient solution containing arsenate, the amount of immigrating free ^{32}P and ^{42}K was found to be reduced to about half their normal values.

The authors wish to express their hearty thanks to Professor NIELS BOHR, the director of the Institute of Theoretical Physics, University of Copenhagen, in which the investigations were carried out, and to Dr. NIELS NIELSEN and Dr V. HARTELIUS for growing the yeast and for determining the survival figures.

SUMMARY

Irradiation with a dose of 30,000 r influences the amount of ^{32}P and ^{42}K migrating daily from the yeast cells into the nutrient solution to a minor extent only. The amount of migrating ^{32}P, not however of ^{42}K, is strongly increased after irradiation with an only partly lethal dose of ultraviolet radiation.

ZUSAMMENFASSUNG

Die Bestrahlung mit 30,000 r beeinflusst die Menge der täglich aus den Gärzellen in die Nährlösung übertretende ^{32}P und ^{42}K Menge nicht wesentlich. Die Menge des übertretenden ^{32}P, nicht dagegen die von ^{42}K, wird nach Bestrahlung mit einer nur teilweise letalen Dosis von ultravioletter Strahlung wesentlich erhöht.

RÉSUMÉ

L'irradiation avec une dose de 30,000 r n'a qu'une action peu marquée sur la quantité de ^{32}P et de ^{42}K passant journellement des cellules de levure dans la solution nutritive. La quantité de ^{32}P émigrant des cellules, mais non, en revanche, celle de ^{42}K, augmente fortement après irradiation aux Rayons ultra-violets avec une dose seulement partiellement mortelle.

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FROM THE RADIUMHEMMET, STOCKHOLM (CHIEF: PROFESSOR E. BERVEN)

FURTHER EXPERIENCE WITH RADIOTHERAPY IN CANCER OF THE CORPUS OF THE UTERUS[1]

by

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The Radiumhemmet method of treating cancer of the corpus uteri by packing the uterine cavity with radium tubes was published in the Acta Radiologica in 1941.[2] When the 1941 report was prepared we had used the packing method as a routine for six years only. Thus, except for the results obtained in a series of 46 patients treated in 1934, we could report on nothing but primary results.

Because of the promising primary results we have used the packing-method ever since. To-day the 5-year results in cases treated in 1934 to 1939 inclusive are available. They are presented in this report and are compared with the result obtained in previous years. The survey of the results is preceded by a brief summary of our system of classification and examination of our patients, of our technique of treatment, and of the rules which we have adopted in calculating the results. Those interested in knowing the details are referred to the above quoted paper.

Histological classification. According to the system developed by REUTERWALL ten different histologic groups are distinguished. Groups 1—6 include the various types of adenocarcinoma. Groups 7 and 8 those of solid carcinoma, Group 9 the uncertain cases in which there is well founded reason to suspect cancer, Group 10 carcinosarcoma and malignant mixed tumours. In the following report cases allocated to Group 10 are excluded. The group 9 cases are included but reported separately. We have made it a rule to enter in our statistics only cases in which our chief pathologist is responsible for the microscopic diagnosis.

Clinical classification. On revising our series of cases of corpus cancer in 1929 we noticed that a considerable number of uterine cancer cases

[1] Submitted for publication, Febr. 18, 1946.

[2] Acta Radiologica 1941, XXII, 2, pp 14—99.

could not be satisfactorily classified as either corpus or collum cancer. In order to get a correct conception of the result of treatment within these two groups we considered it advisable to exclude the debatable cases. They have since been allocated to separate groups, the first of which includes cases with a coincident involvement of the corpus and the collum, the second cases with a coincident involvement of the uterus and the ovaries, and the third with a coincident involvement of several pelvic organs. The threee groups are called: cancer corporis et colli uteri, cancer uteri et ovarii, and cancer pelvis. Cases referred to either of these three groups are not included in this report.

Concerning the further grouping of corpus cases we retain the classification into clinically operable, technically operable and inoperable cases. A patient is registered as technically operable if a bad operative risk because of pronounced adiposity or old age or some associated disease such as heart condition, diabetes, hypertension, and such like.

Examination. In all cases which we nowadays classify as cancer of the corpus uteri the clinical diagnosis is based on the result of a fractional curettage.

Radiotherapeutic technique. Prior to 1930 we treated our cases of corpus cancer by introducing in the uterine cavity a single tube containing between 35—45 mg radium element, enclosed in a lead filter equivalent to 3 mm of lead. The patient was irradiated twice, with an interval of three weeks between the first and the second treatment. Each time about 1.200 mg element hours were administered. Because of the poor results obtained by using a single narrow and powerful tube we gradually elaborated in 1930—34 the packing-method, whereby the uterus is packed with less powerful tubes of equal size and shape and sufficient in number to get the uterine cavity compeletely filled.

Instruments. As mentioned in the 1941 report the radium tubes used in packing have an external length of 20 mm and an outside diameter of 2.8 mm, a wall thickness equivalent to 1 mm of lead (0.35 mm Au + 0.3 mm Pt) and contain each 8 mg of radium element. Each tube is put in an additional filter, the size of which varies according to the width of the uterine cavity. In the 1941 report four sizes of additional filters are mentioned differing in respect to their external diameter which is 7.8 mm, 9.8 mm, 11.8 mm, and 13.8 mm respectively.

At the time of the previous report we still used a single powerful tube in case of a small and narrow uterine cavity. In recent years we have found it suitable to apply the packing method to such cases also.

For that reason we have developed two sets of small additional filters with an outside diameter of 5.1 mm and 6.3 mm respectively and 18 mm in length. In order to obtain the desired smallness the lead filter has been substituted by gold, equivalent to two mm of lead.

The radium tubes previously used are too big to fit these small additional filters. Instead we use needles with an outside diameter of 2.3 mm and 14 mm in length. Each needle contains 10 mg radium element enclosed in a primary filter of 0.2 mm gold + 0.3 mm platinum.

The technique of application has not been altered. We have noticed that generally little difficulty is encountered in determining beforehand not only the suitable size but also the approximate number of additional filters necessary for a complete filling of the uterus in the individual case.

Experience and caution is required in order to pack the uterus satisfactorily. The technique of application is, however, not difficult. For the last few years most cases have been treated by junior assistants, who have no previous experience from the technique of packing. Nevertheless accidents have been rare. In addition to the case mentioned in the previous report on page 44 the following two cases may be mentioned.

1942. No. 12169. Hopeless and inoperable case of adenocarcinoma in a large myomatous uterus. Corpus fixed in the small pelvis in pronounced retroflexion. Lymph-node metastases in the groins. Great difficulty is encountered in passing the cervical canal. On applying the radium the steel string of the second irradiator was broken and the irradiator had to be removed by laparotomy and hysterotomy. Patient died from peritonitis following operation. Autopsy revealed multiple large metastases in the pelvic and abdominal lymph-nodes, in the liver and in the vertebrae.

1943. No. 5847. Adenocarcinoma of the corpus. Uterus the size of a fist enlarged by multiple fibroids. In spite of the presence of a perforation an attempt was made to pack the uterus with radium. Control by roentgenogram showed three irradiators situated outside the uterus. Removal of radium, total hysterectomy, uncomplicated recovery. Patient still alive and free from evidence of the disease.

Method of treatment. Primary radiological treatment, in case of failure combined with surgery is the routine method of treatment at the Radiumhemmet in cases of cancer of the corpus. Primary surgical interference is resorted to in occasional operable cases, for instance a corpus cancer combined with large fibroids or with an ovarian tumour.

In each case radium is applied twice with an interval of three weeks between the first and the second application. The time during which the radium remains in the uterus varies with the number of irradiators applied and the size of the additional filter chosen. The treatment time as calculated by BENNER is given in the 1941 report and in the table attached at the end of this paper. Roentgen irradiation is administered in case the uterus is fixed or else if the tumour has spread to the surroundings of the uterus.

Five-year result of treatment. During the period 1914 to 1939 inclusive 698 patients suffering from cancer of the corpus have been examined at the Radiumhemmet gynecological clinic with a view to treatment. 670 patients were submitted to treatment. In 28 cases treatment was considered unsuitable owing, in the majority of cases, to the extent of

the disease or to the patient's bad general condition; the cases are evenly distributed over the whole period.

363 patients were alive and free from evidence of the disease five years after the beginning of the treatment. 320 patients have been examined at the clinic at the end of the 5-year period, whereas 43 have been examined by physicians outside the clinic or have reported on their condition by letter.

Table 1.

Absolute and over-all relative cure rate in the treatment of corpus cancer at the Radiumhemmet 1914 to 1939 inclusive, estimated after a period of 5 years from the beginning of treatment.

Total number of cases examined	698
Free from evidence of the disease	363
Absolute cure rate	52.0 %
Number of cases treated	670
Free from evidence of the disease	363
Relative cure rate	54.2 %

Table 1 shows an absolute cure rate of 52 per cent. Of the 363 cured patients 44 belong to the histologic Group 9, and in 49 patients hysterectomy was performed because of failure of radiotherapy.

Table 2 shows the result obtained by our previous technique of treatment compared with the result obtained by the packing method. As mentioned above the latter has been used as a routine since 1934.

Table 2.

Result of treatment.

	1914—1933	1934—1939
Total number of patients treated	354	316
Alive without evidence of the disease after a period of observation of 5 years	158	205
Relative cure rate	45.0 %	64.9 %

From Table 2 it is evident that the 5-year result obtained in 1934—1939 is better than that of 1914—1933 the cure figure being raised by 20 per cent.

There is a slight variation in the distribution of clinically operable, technically operable, and inoperable cases in the two series. The difference in the cure rate between the first and the second period is

for the clinically operable cases	16.3	per cent
for the technically operable cases	18.9	» »
for the inoperable cases	20.9	» »

It should further be noticed that in the 1914—1933 series there are 29 Group 9 cases of a total of 354, *i. e.* 8.2 per cent and in the 1934—1939

series 15 of a total of 316 *i. e.* about 4.7 per cent. Finally, in the period 1914—1933 patients operated upon after failure of radiotherapy number 27 (17 per cent of those cured) whereas in the period 1934—1939 there are only 22 such cases (10.7 per cent). Consequently we have reason to believe that the noticeable improvement of the result of treatment should be accredited to the packing method.

The 1941 repor includes an analysis of the results obtained by hysterectomy in operable cases of corpus cancer. Judging from available statistics the 5-year cure rate in operative treatment is 55 per cent or less. The following sentence may be quoted from the 1941 report: »Should we succeed permanently to obtain in our clinically operable cases by the packing method a cure rate of about 60 per cent we would be justified in concluding that it is possible to obtain better results by radiotherapy alone than by surgery alone. This is still more probable as in our series there are included a number of cases which at laparotomy would have been found inoperable and which would not have appeared in a surgical statistic.»

The 1934—1939 series includes 153 cases registered as clinically operable. 115 of those are alive and free from evidence of the disease after a period of 5 years. 102 of the 115, or 66.7 per cent of the total, were cured by radiotherapy alone. By this result the above conclusion has attained additional support.

Conclusions as to the value of primary hysterectomy plus postoperative irradiation compared with that of primary radiotherapy plus hysterectomy in case of failure should be postponed until significant statements concerning the results of the first mentioned method are available.

Duration of treatment (by S. Benner)

The treatment time required when using the new small irradiators is calculated in the manner previously described in the Acta Radiologica 1941. Because of the smallness of the irradiators and of the packs composed by them, the technique of measurement has been, however, somewhat modified. The irradiators were held together in packs by strips of adhesive plaster and put on a sheet of paper. The contour of the pack was drawn in pencil and a number of points were marked 15 mm outside this contour. The condenser chambers were placed on these points and were irradiated for a suitable length of time. The radiation intensity was calculated from the loss of charge of the chambers. For further control, a roentgen-photo was taken each time of the pack lying on the paper and of the measuring points marked by small metal objects.

The result is given in Table 3.

Table 3.

Average intensities in Imc for different numbers of irradiators of different sizes, and appropriate treatment times calculated therefrom.

Number	Irradiators No.			
	0.0 [1]		0.5	
	Intensity	Hours	Intensity	Hours
5	8.0	16	—	—
6	8.6	14¾	7.9	16
7	9.2	13¾	8.6	14¾
8	9.8	13	9.3	13¾
9	10.5	12	10.0	12¾
10	11.2	11¼	10.7	11¾
11	—	—	11.4	11
12	—	—	12.0	10½

[1] The previously used additional filters being marked 1, 2, 3 and 4 the new filters have been marked 0.0 and 0.5 respectively.

SUMMARY

Report on result of treatment of cancer of the uterine corpus by the Radiumhemmet method of packing the uterine cavity with radium tubes. A relative over-all 5-year cure rate of 64.9 per cent was obtained by the packing-method in a series of 316 patients, the corresponding figure in a series of 354 previously treated patients being 45 per cent.

ZUSAMMENFASSUNG

Bericht über die Ergebnisse der Behandlung des Corpuskarzinoms mit der im Radiumhemmet verwendeten Methode: Vollpacken der Uterushöhle mit Radiumröhrchen. In einer Reihe von 316 Kranken wurde mit der Vollpackungsmethode eine relative 5-jährige Heilung von 64.9 % erzielt. In einer Reihe von 354 früher behandelten Kranken war die entsprechende Zahl 45 %.

RÉSUMÉ

Rapport sur les résultats du traitement du cancer du corps utérin par la méthode en usage à Radiumhemmet qui consiste à remplir la cavité utérine de tubes de radium. Sur l'ensemble des cas une proportion relative de 64.9 % de guérisons d'une durée de 5 ans a été obtenue par cette méthode dans une série de 316 malades, le chiffre correspondant, pour une série de 354 cas traités précédemment, étant de 45 pour cent.

FROM THE ROENTGENOLOGIC SERVICE OF SERAFIMERLASARETTET, STOCKHOLM, SWEDEN
(CHIEF OF SERVICE: PROFESSOR E. LYSHOLM)

THE REGISTRATION OF THE MOVEMENTS OF THE HEART WITH GEIGER-MÜLLER COUNTERS AND SYNCHRONOUS ELECTROCARDIOGRAPHY [1,2]

by

Gunnar Hjelmare

Experiments aimed at achieving more accurate roentgenologic registration of the movements of the heart than that provided by ordinary kymography have been under way at the Roentgenologic Service of the Serafimer hospital since 1937. During the years 1937 to 1939, we worked with photoelectric cells on the principle that the photoelectric cell recorded the variations in intensity of the fluorescent light which appeared on the fluorescent screen in screening the heart. However, the combination of fluorescent screen and photoelectric cell was found to have so many disadvantages that the experiments had to be abandoned. It was therefore found necessary to resort to another type of radioactive indicator, the Geiger-Müller counter.

During recent years increasing use has been made of Geiger-Müller counters in scientific and technical work for the registration of radioactivity and of roentgenradiation. They have also proved useful in medicine. Two papers have been published on the determination of the circulation time by members of the staff of this Service (LYSHOLM, SOHRNE and WICKBOM). There Geiger-Müller counters were used as detectors of radioactive radiation from Na^{24} (sodium 24). Attempts to use these counters instead of film in roentgen diagnostics have also been made here. At first the tedious system of counting the individual Geiger-Müller impulses was followed, the pulses being recorded through an amplifier on a counting clock. In 1942 an amplifier was constructed with the help of FREDHOLM and FREDZELL, which permitted registration of the intensity of the roentgen rays in the form of a continuous tracing on a film strip. This apparatus has been used in investigations on circulation times by

[1] Submitted for publication, Febr. 28, 1946.
[2] This work was aided by a grant from the Rockefeller foundation.

means of injections of contrast fluid and for the measurement of minimal absorption differences that could not be visualized on an X-ray film. The results of these studies were published by LYSHOLM in the *International Review of Radiology* in 1942.

The Geiger-Müller counter generally consists of a glass tube with a central wire, the anode, enclosed in a concentric metal cylinder, the cathode. The tube is filled with a suitable gas or gas mixture. The tube is connected with a high resistance to a high tension supply of about 1,000 volts D. C.

For our purposes we constructed new types of tubes filled with vapors of organic metal compounds, whose absorption of roentgen rays is many times that of the gases hitherto used in these tubes.

When the roentgen rays meet the cathode of the Geiger-Müller counter and penetrate to the gas, electron avalanches occur and are manifested as current impulses of exceedingly short duration. The number of impulses emitted per time unit is in proportion to the intensity of the incident radiation. The impulses from the Geiger-Müller counter are transmitted through an integrating D. C. amplifier to a recording milliamperemeter or galvanometer. In the present experiments we used an ordinary electrocardiograph (ELMQVIST system) with four galvanometers, two of which could be switched directly to input terminals, excluding the amplifiers.

It is thus possible to record, concurrently with a kymogram,[1] an electrocardiogram from three leads on the same registering paper or else two kymograms (*e. g.* one from a point on the wall of the heart and one from the aorta) and one electrocardiogram from one lead.

The Geiger-Müller counter is enclosed in a lead envelope with a longitudinal slit measuring about 30 × 4 mm, and is applied with the slit at right angles to the contour of the heart over the point whose movement is to be recorded, so that about half the length of the slit is shadowed by the heart. The movement of the shadow of the heart back and forth in the slit causes corresponding variations in the incident radiation and thereby in the counter impulses, which are transmitted by the amplifier to corresponding galvanometer readings.

The Geiger-Müller counter is placed next to the body surface with the help of a fluorescent screen in the manner described above and is fixed there at right angles to the roentgen rays. Thereafter the aperture is stopped down to a field about 50 mm in diameter, measured on the fluorescent screen. The center point of the slit is in the path of the central ray. The focus-Geiger-Müller counter distance is about 80 cm. A 1-mm aluminum filter is used during the application of the counter as well as during the recording. An electrocardiogram is taken at the same time in the usual way in three leads.

[1] Note that this is not an ordinary X-ray kymogram but a sort of kymogram taken with a Geiger-Müller counter.

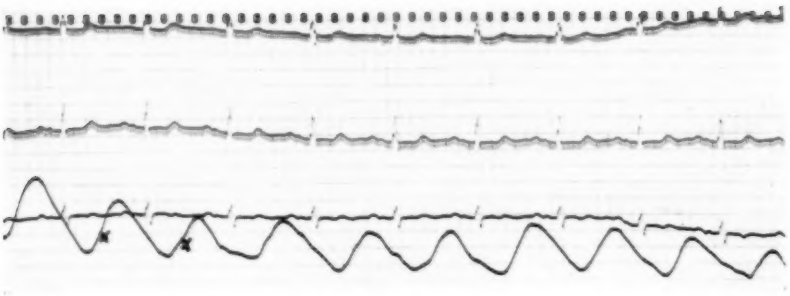

Figure 1. Slit over the left heart contour in p.a. projection. Respiration suspended. (×) systole.

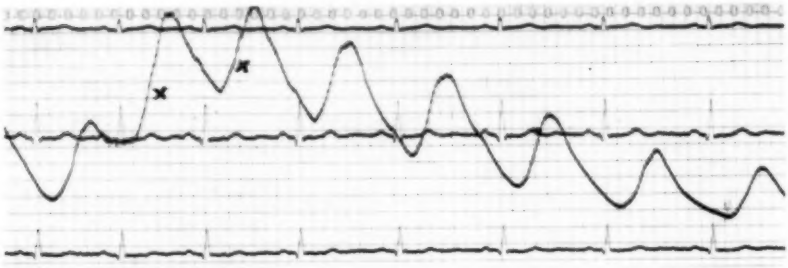

Figure 2. Slit over left heart contour in p.a. projection. Left side, inspiration; right side, expiration. (×) systole.

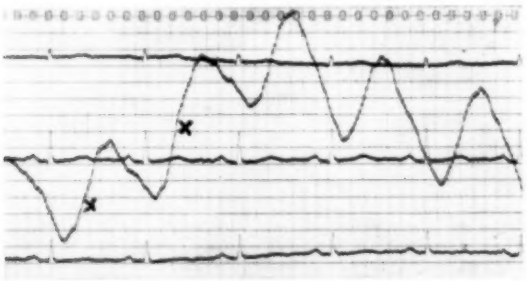

Figure 3. Slit over left heart contour in p.a. projection. Left side, inspiration; right side, expiration. (×) systole.

Hitherto the examination has been made on patients in the supine position only. At the beginning of the recording the patient holds his breath. After a number of heart movements have been recorded, the

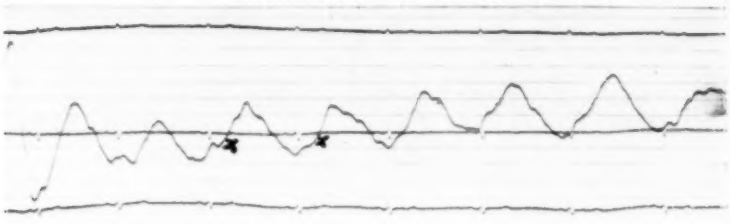

Figure 4. Slit over right contour in p. a. projection. Respiration suspended. (×) systole.

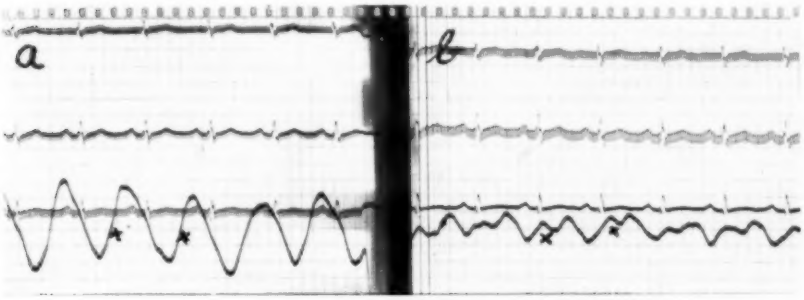

Figure 5. Patient with right-sided pneumothorax.
a) Slit over left contour in p.a. projection.
b) Slit over anterior contour in second oblique projection. Respiration suspended. (×) systole.

patient is allowed to breathe again until the examination is completed. In most of the cases we succeeded in registering the heart movements despite the respiration movements of the patient. About thirty patients were examined, generally in conjunction with a routine roentgen examination of the heart. At first we always chose a subject in whom screening showed the pulsations to be especially strong. It became evident, however, that clear readings could be secured even with small pulsations, at least in the left contour of the heart. Hitherto, most of the examinations of the movements of the left contour have been made with a sagittal projection, although a number of recordings have also been made with an oblique projection. Examples of the curves recorded together with technical data are shown in the accompanying figures. The movements of the contour in the medial direction are labelled systole, those in the lateral direction diastole.

As appears from the illustrations, this method would seem to offer a possibility of establishing with hitherto unsurpassed accuracy the time

correlation between the kymogram and the electrocardiogram at least for certain parts of the heart. The scientific interest of the method as a means of broadening our knowledge of the working mechanism of the heart is, therefore, apparent. However, in view of the limited number of cases studied, the time is not yet ripe for any discussion of physiologic or, even less, clinical problems that may arise in this connection. We are working further to improve the method and to evolve a system of recording simultaneously the movements of different parts of the heart with two Geiger-Müller counters. It is our intention to describe at a later date the experiences which may be gained from the application of this method of examination.

The Geiger-Müller counters, as well as the apparatus for tension stabilization and amplification, were designed and constructed by Helge Fredholm, a civil engineer, who also collaborated in working out the method.

SUMMARY

A brief survey of the experiments of the past years with photoelectric cells and Geiger-Müller counters at the Roentgenologic Service of Serafimerlasarettet is followed by a description of a method of using Geiger-Müller counters to register the movements of the heart during screening with concurrent electrocardiography.

ZUSAMMENFASSUNG

Nach einem kurzen Rückblick auf die in den letzten Jahren in der Röntgenabteilung des Serafimerkrankenhauses betriebenen Versuche mit Photozellen und Geiger-Müllerschen Röhren wird eine Methode beschrieben, unter Durchleuchtung die Bewegungen des Herzens mit der Geiger-Müller'schen Röhre zu registrieren und gleichzeitig ein Ekg aufzunehmen.

RÉSUMÉ

Après un coup d'œil rétrospectif sur les essais faits ces dernières années avec des cellules photo-électriques et des tubes de Geiger-Müller, dans le Service de Radiologie de l'Hôpital des Séraphins, l'auteur décrit une méthode permettant d'enregistrer, sous radioscopie, les mouvements du cœur avec le tube de Geiger-Müller, et de prendre en même temps un électrocardiogramme.

FROM RADIUMHEMMET, STOCKHOLM (CHIEF: PROF. E. BERVEN)

RESULTS OF TREATMENT WITH RADIOTHERAPY IN CARCINOMA OF THE PROSTATE[1]

by

Sven Hultberg

Of recent years a number of articles have been published concerning improvement of the palliative results of the treatment of cancer of the prostate with operative or radiological castration and with estrogenic hormone therapy (EMMETT & GREENE, HERBST, HUGGINS, LANE, MUNGER and NESBIT, PAZZOS & CUMMINGS). In two lectures delivered to The Swedish Surgical Society in 1944 and 1945 (published in Nordisk Medicin) ROMANUS has given an account of the first attempts at Karolinska Sjukhuset to apply this therapy as an adjuvant to the treatment resorted to earlier. — In order to enable a comparison with the results that we hope to achieve with the hormone therapy I have therefore brought together *Radiumhemmet's material of irradiated cancer of the prostate during the period 1929—1940*. During this period no deliberate castration has been undertaken, neither operative nor radiological; on the contrary, the testicles have been carefully protected against the irradiation with a lead capsule or lead rubber plates having a filter value of 3—6 mm Pb.

In all the literature concerning cancer of the prostate there is an entire unanimity on the point that definite cure has only been brought about with radical operation, and that it is only in a few cases that this has been possible to realize. The majority of patients do not visit a doctor until the tumour has already become inoperable. A sufficiently *early diagnosis is difficult*, and the cases that have been operated upon with a good result have often been those in which the preoperative diagnosis has been hypertrophy of the prostate, but the histological examination has afterwards shown the presence of a cancer.

The radiation therapy of cancer of the prostate is therefore above all a treatment of cases which have been considered inoperable with or without the occurrence of metastases, and in addition a postoperative therapy in cases that have been operated upon either radically or only

[1] Submitted for publication, Febr. 15, 1946.

with partial removal of the cancer. — Definite cure of cancer of the prostate through irradiation only has not, as far as I have been able to ascertain, been described in any case, and the radiological treatment has always been obliged to aim at only palliative help. Every addition to this is therefore to be greeted with satisfaction. But the chief desideratum still remains to find a method for an early and reliable diagnosis of this disease, in order to increase the possibilities of a radical cure.

During the period 1929—1940 167 patients with cancer of the prostate came to Radiumhemmet for treatment, and of these 60 had previously been operated upon. They had all been sent to Radiumhemmet by some head physician, as a rule a surgeon, and they had come from various parts of the country in Radiumhemmet's extensive reception region in northern and middle Sweden. The operations had therefore been carried out by a number of different surgeons.

The age-distribution was as follows:

< 50;	50—55;	55—60;	60—65;	65—70;	70—75;	75—80;	80—85 years
1	12	21	33	40	35	21	4

We thus see that about $^1/_4$ of the cases were aged between 65—70 years and $^2/_3$ between 60—75 years, and that 13 patients (= 8 %) were under 55 years of age. By way of comparison it may be mentioned that in a post-mortem material of 292 cases RICH reports 37 % as being between 75—80 years and 28 % between 70—75 years old.

By investigation of Radiumhemmet's patients with cancer of the prostate it has proved suitable to divide them up into three different groups:

1) *patients who have proved to be inoperable;*
2) *patients who have been operated upon and sent up for postoperative treatment* as soon as possible after the operation;
3) *patients with recurrences or metastases after an earlier operation.*

1) Of the 167 patients *107* were regarded by the surgeon who had sent them up as *inoperable*, amongst which number an explorative sectio alta had been carried out in 4 cases. Patho-anatomical diagnosis had been made in only 15 of these 107 cases, and the microscopic diagnosis had been performed on samples taken with transurethral electro-resection or on post-mortem. In the remaining 92 cases the diagnosis had been made in the light of the clinical examination, and in this material for investigation I have only included those cases in which both the surgeon who sent in the case and Radiumhemmet's physician have been in full agree-

ment regarding the diagnosis. The correctness of the latter has in practically all cases been confirmed either by the existence of skeletal or glandular metastases already on admittance or by the appearance of such in the sequel, or by the decease of the patients owing to a local progress of the cancer.

These 107 patients had only undergone radiological treatment, and of their number

49 = 45 %	died	within	1	year
33 = 31 %	»	»	1—2	years
8 = 7 %	»	»	2—3	»
11 = 10 %	»	»	3—5	»

We thus see that about $^3/_4$ died within 2 years after the inception of the treatment. — 5 patients (= 4½ %) lived between 5—10 years and 1 patient 11 years. *Thus altogether 17 patients (= 16 %) lived for more than 3 years, and 6 patients (= 5.6 %) for more than 5 years after the irradiation treatment*, and this must be considered a fairly good result.

As histological verification was lacking in the majority of cases the suspicion immediately arises that in the 17 cases where the patients survived the treatment by more than 3 years it was not a matter of cancer but only of hypertrophy of the prostate. I have therefore felt it incumbent upon me to give a rather more detailed account of these cases. — We then find that *patho-anatomical diagnosis showed adenocarcinoma or cancer simplex in 5 cases*, and that *skeletal metastases occurred in a further 8 cases*. — Explorative *sectio alta had been carried out on 2 patients* and revealed an inoperable cancer that had grown up along vesicula seminalis and infiltrated the surrounding pelvic tissues. — *One patient died owing to local progress* of the cancer after having been subjectively practically free of any discomfort for about 2½ years. Despite continued radiation therapy the condition grew steadily worse, and the patient died after a further period of about six months. — All of these cases died from their cancer except 3, and of the latter one patient died of heart failure (he was one of those who had undergone an explorative sectio alta), and 2 are still alive. These 2 survivors both have histologically confirmed diagnosis (electro-resection) of cancer solidum and adenocarcinoma respectively, one of them from samples taken both in 1940 and 1945! — *The remaining patient* died of heart failure in his home 6 years after the treatment, and unfortunately no post-mortem was performed; but the diagnosis was regarded both by Prof. KEY and Prof. BERVEN as absolutely beyond doubt, and the patient had, moreover, later been examined by a number of other physicians, who all considered it to be a case of cancer. On palpation per rectum, namely, one found a hard, nodular resistance in the right lobe of the prostate, while

the left lobe was soft. From the tumour was felt a hard infiltrate spreading out towards the pelvic wall and up along the right seminal vesicle. The patient was given teleradium treatment in 3 series during the years 1935—36, after which he was practically free of discomfort. In the summer of 1939 his symptoms returned, and in spite of further treatment his condition grew worse, and it gradually became possible to observe considerable progress of the tumour in the pelvis. The patient died, however, of heart failure in 1941.

2) During the period covered by the investigation 46 patients were sent to Radiumhemmet for *postoperative radiation treatment*. Of these, by the surgeon responsible for the operation, 15 were considered to have been radically operated upon, while in the remaining 31 cases it had not been possible completely to remove the malignant tumour.

a) The difficulty of diagnosing carcinoma prostatae early is well exemplified by the fact that of the *15 cases radically operated upon* 12 had undergone operation under the diagnosis of hypertrophy of the prostate, and only 3 under the diagnosis of cancer. In 3 of the 12 cases, however, the operating surgeon had suspected the presence of cancer in the course of the operation. In the remaining 9 cases the histological diagnosis came as an unpleasant surprise.

I *8* cases only roentgen treatment from 2 anterior and 2 posterior fields, as a rule with 2,000 to 2,400 r to each field, was administered as *postoperative treatment*. In *4* cases additional treatment was given in the form o˙ teleradium from a perineal field with a dose of 2,000—3,600 r. In *3* cases the patients were treated only with teleradium from altogether 5 fields with doses varying from 2,000 to 4,000 r.

Of the 15 patients, 2 died within 1 year after the operation, 3 within 1—2 years, 6 within 2—3 years and 2 within 3—5 years after the operation, while 4 survived for more than 3 years and 2 patients for more than 5 years.

b) Of the 31 patients *upon whom it was not possible to operate radically* the operation was performed under the diagnosis of cancer only in 6 cases, and under the diagnosis of hypertrophy of the prostate in 20 cases, while in the remaining 5 cases the preoperative diagnosis was not mentioned in the protocol. Thus here, too, we have evidence of the difficulty in making a correct diagnosis, despite the fact that in these cases the disease was rather far advanced.

On *2* occasions *the treatment* has consisted in the application of radium tubes of 50 mg in the prostatic bed, in one case 2 tubes, in the other 1 tube for a period of 10 hours. The first-mentioned patient died 10 days after the treatment from rising infection of the urinary passages. — The other patient received additional roentgen treatment from 4 fields but died of metastases 14 months later.

4 patients were given only teleradium, *10* only roentgen and *15* combined roentgen and teleradium with doses of the same magnitude as for the cases radically operated upon. On some occasions, however, somewhat larger doses were administered: 2,800 r from the roentgen field and 4,500 r with teleradium. — As a rule the patients have come for postoperative treatment within a few weeks after the operation.

10 patients died within 1 year after the operation, 5 within 1—2 years, 8 within 2—3 years and 5 within 3—5 years. *8 patients have survived for more than 3 years, and 3 for more than 5 years of the 31 cases not radically operated upon.* — One can scarcely venture to draw any comparison between the results of the treatment of the cases radically operated upon and those incompletely operated upon, as the figures are too small to allow of any definite conclusions.

3) As a *third group* I have assembled the cases that had been operated upon earlier but not sent in for postoperative treatment, and that did not come to Radiumhemmet until *recurrence in loco or metastases* had been observed. This group comprises altogether 14 patients, of which number only one had been operated upon under the diagnosis of cancer, the others having been operated upon under the diagnosis of hypertrophy of the prostate. Patho-anatomical diagnosis showed cancer in 7 cases and »typical adenoma» in the remainder. On the occasion of a later operation the patho-anatomical diagnosis of cancer was made in 2 cases among these »adenomata». The operation was considered to be radical in 12 of these 14 cases.

Recurrence or metastases had been observed after the operation within 1 year in 2 cases (not rad. op.), within 1—2 years in 3, within 3—4 years in 5, within 5—6 years in 2, within 7—8 years in one and after 15 years in one case. — The last-mentioned patient was operated upon in 1924 under the diagnosis of hypertrophy of the prostate, and the patho-anatomical diagnosis showed »adenomatous hypertrophy with strong suspicion of incipient cancer degeneration». — In 1939 a recurrence in loco was observed, for which the patient was treated with teleradium with 2,700 r from each of 4 fields and 2,000 r from one perineal field. During the years 1940—43 additional treatment was given from the same fields with one series annually and a dose of 1,300—2,000 r each time. — In June 1944 skeletal metastases appeared, which were treated with roentgenrays. The tumour then showed considerable local progress with perforation to the rectum. The patient died of the cancer in July 1945, 21 years after operation, and $5^{3}/_{4}$ years after the treatment of the recurrence had been commenced.

In *6* cases the radiation treatment given has consisted of only roentgen, in *3* cases of teleradium and in *4* cases of a combination of both methods, and the dosage has been the same as that described above.

In *one* case 9 radium needles of 10 mg were implanted in the local recurrence for a period of 5 hours in connection with renewed operation. This patient died of infection of the urinary passages 4 months later.

Of the 14 patients who all died of their cancer, 4 died within 1 year, 7 within 1—2 years, 1 within 2—3 years and 1 within 3—5 years *after the treatment of the recurrence*. Only the patient of whose case a more detailed account is given above survived for more than 5 years.

If we consider *the length of life of all the patients operated upon* (60), we find that *after the operation* 13 died within 1 year, 10 within 1—2 years and 14 within 2—3 years, while *23 patients* (= *38* %) *survived for more than 3 years after the operation and 12* (= *20* %) *for more than 5 years*. Thus a better result than from radiation treatment of the *inoperable cases, where only 16* % *survived for more than 3 years and 5½* % *for more than 5 years*. — The average age of the inoperable patients proved to be 65½ years, and 66½ years of the patients operated upon. This small difference in age cannot therefore have had any influence on the difference in the result between the two groups of cases. Instead I think we have to explain this discrimination by means of the circumstances, that among the patients operated on were no metastases by the admittance, while among the inoperable patients they could be found in half of the cases. These men appeared then in a more advanced stadium and because of this their chances to a more lasting improvement were bad.

Of the 60 patients operated upon only 10 had been preoperatively diagnosed as cancer cases, while in the remaining cases the diagnosis was not made until after the commencement of the operation or else through the histological examination of the preparation.

It is remarkable that in 7 cases the operative preparation did not show cancer, although the course of the disease in the sequel revealed the fact that a cancer had existed. This may be explained, however, in the light of the fact that all the patients were operated upon through a *supra-pubic sectio alta*, which does not afford such a good survey of the operative field as a perineal exposure. A cancer growing in the so-called surgical capsule, *i. e.* the prostatic tissue proper that has been displaced by the adenoma, may then escape discovery when this »capsule» is left behind after a sectio alta prostatectomy. When this method is applied one is confronted with considerable technical difficulties in completely loosening out a prostate if the surgeon suspects in the course of the operation that a cancer is present. — As it has proved difficult to diagnose cancer of the prostate at an early stage it may be discussed whether a perineal exposure of the prostate should not be undertaken in a considerably greater number of cases than is now usual in Sweden, as in this way one would certainly be able radically to remove a carcinoma prostatae

more frequently than is now the case. An electro-resection per urethram or an urethrography might possibly, it is true, in a number of cases contribute towards an earlier discovery of a cancer, but bearing in mind the fact that it is rather seldom that the latter begins in the periurethral part of the prostate, a radical surgical operation remains as our best chance of more permanently improving the result of treatment of this common ailment; and such an operation can scarcely be performed via a supra-pubic sectio alta, as has also been pointed out by WILDBOLZ, YOUNG and HELLSTRÖM.

The more difficult operation with a perineal prostatectomy is further motivated by the circumstance that among all the patients with an enlarged prostate the presence of cancer has been shown in about 20 % of the cases (YOUNG, MOORE).

As it may be of a certain interest to consider in greater detail the patients who either had *metastases* on admittance or developed them in the sequel, I have made a special grouping of these. We then find that *on admittance* to Radiumhemmet *of the 167 patients 57 had metastases.* These were localized in the following way:

skeletal metastases in 41 cases;
glandular metastases in groins or fossae iliacae in 12 cases;
glandular and skeletal metastases in 3 cases;
pulmonary metastases in 1 case.

Further, in 4 patients the cancer had grown through the wall of the bladder or intestine. — Of all these 61 patients 36 died within 1 year, 20 within 1—2 years, 2 within 2—3 years and 3 within 3—4 years after admittance.

Of the remaining 106 patients, who on admittance to Radiumhemmet had no demonstrated metastases, 48 proved to have metastases in the sequel, and of this number 38 were skeletal metastases. The period of survival for these was as follows: 26 died within 1 year, 16 within 1—2 years, 4 within 2—3 years, 1 within 3—4 years, while 1 patient survived for 7 years after the first observation of metastases.

If we collate the two groups we get the following table of the periods of survival for these 61 + 48 = 109 patients from the point of time when metastases were observed:

62 = 57 %	died	within	1	year
36 = 33 %	»	»	1—2	years
6 = 5½ %	»	»	2—3	»
4 = 3½ %	»	»	3—4	»
1 = 1 %	»	»	7—8	» .

We thus see that only 10 % of the cases with metastases survived for more than 2 years, and yet this figure must nevertheless be said to constitute a rather good result of the life-prolonging effect of the roentgen treatment of these doomed patients.

As regards *the treatment*, no deliberate castration or hormone therapy has been applied in these 167 cases, as has already been remarked. On the contrary, the testicles have been protected from the radiation as carefully as possible. Such protection is certainly sufficiently effective in connection with roentgen treatment, but where teleradium has been administered from a perineal field the effectiveness of the protection against the irradiation may be questioned, and it is possible that in some cases an unintentional castration has resulted, with consequent beneficial effect for the patient in question.

1) *Roentgen treatment* alone has been applied in 70 cases, *during the earlier years as a rule with repeated series* from 2 anterior and 2 posterior fields *towards the region of the prostate*, and in 32 cases also from an additional field in the perineum. The dose to each field has then varied between 600—1,200 r during each series with daily doses of 200—350 r. The field-size has usually been 100—150 cm^2. As filter $^1/_2$ Cu 1 Al or Thoraeus's Sn-filter has been used, 180 kV and 10—20 mA, and the distance between focus and skin has been 50—60 cm. The series have been repeated at intervals of 2—4 months. *During the later years* we endeavoured to give the patients as large a dose as possible during the first series, with total doses of 2,000—2,800 r per field and daily doses of 400—500 r. Only in cases where there was a troublesome reaction in intestine or bladder, or where the patient could not stand up to the treatment owing to general tiredness or sinking number of blood cells did we content ourselves with 1,500—2,000 r, and then instead gave an additional dose of 800—1,600 r 3 to 4 months later. Nowadays we also as a rule increase the total dose by giving 2,500—3,000 r from a perineal field with the teleradiumbomb.

In the cases of *the skeletal metastases* the dosage has varied between 1,200—2,400 r per field at intervals of 4—8 months. The palliative pain-relieving effect has often been surprising, and after only a few treatments life has become more tolerable for the patients.

Of the 70 roentgen-treated patients 30 died within 1 year, 23 within 1—2 years, 8 within 2—3 years, 8 within 3—5 years and 1 patient within 5—10 years after the beginning of the treatment. *Only 9 survived for more than 3 years after the irradiation.*

2) *Teleradium* with the 3 gr or 5 gr telecurietherapy apparatus has been given in 25 cases with a dosage of between 2,000—4,500 r per field,

and the treatment has as a rule been applied from 2 anterior and 2 posterior fields and 1 perineal field.

Of these 25 patients 10 died within 1 year, 7 within 1—2 years, 2 within 2—3 years, and 2 within 3—5 years, while *4 survived for more than 5 years and 6 for more than 3 years* after commencement of the treatment.

3) *Combined teleradium and roentgen treatment* has been given to 65 patients, the teleradium being applied as a rule towards the perineum. In the other cases in which teleradium has been used this has been as irradiation towards glandular metastases in the groins or fossae iliacae. — 2,000—3,600 r has been given from the perineal field, while the metastases have been treated with a dose of up to 4,500 r. — The roentgen dosage as described above.

Of these 65 patients 20 died within 1 year, 17 within 1—2 years, 12 within 2—3 years, 9 within 3—5 years after the beginning of the treatment, while *7 have survived for more than 5 years and 16 for more than 3 years.*

4) *Radium* has been administered *locally* in 4 cases, needles being implanted in the prostate in one case (earlier described on p. 344), and 1 or 2 tubes of 50 mg radium being applied in the prostatic bed for 8—10 hours in 3 cases. One of these 3 patients died 10 days after the operation, the other 11 months and the third 14 months afterwards. In the two last-mentioned cases roentgen-treatment was given in addition. During the last 10 years this form of therapy has not been resorted to, owing to our own unpleasant experiences as well as those of other radiologists (KEYES, FERGUSON), with infection and necrosis as disagreeable complications.

Two patients had only received a few roentgen or teleradium treatments when these had to be broken off owing to *sudden change for the worse.* Both these patients died of uremia about a week after admittance.

One patient requested the discontinuance of his roentgen treatment after only 3 applications. He died $1^1/_2$ months later.

As regards *the result* of the treatment, it had in 22 cases not led to any improvement of *the urinary symptoms*, while among the remaining patients there were all stages from inconsiderable improvement within a short space of time to considerable improvement in the course of several years. In 22 cases complete subjective freedom from symptoms for a longer or shorter period was registered. — During the reaction period after the irradiation the discomfort always increased, with more frequent urinations and smarting or pain in connection therewith. These symptoms, however, it was possible to alleviate considerably with drugs of opium or belladonna.

The pains connected with the skeletal metastases were alleviated in the great majority of cases where roentgen treatment could be carried out, and complete freedom from pain for about a month up to 2 years was noted in 15 of these 82 patients with skeletal metastases.

The period of survival has already been mentioned in connection with the description of the various groups, but if we compare the results with a view to the various therapeutic techniques we get the following table:

Treatment	Died within 1 year	Died within 1—2 years	Survived for 3 years	Survived for 5 years
Rtg. (70 p.)	43 %	33 %	13 %	1.4 %
Telerad. (25 p.).....	40 »	28 »	24 »	16 »
Rtg. + telerad. (65 p.).....	31 »	26 »	25 »	11 »

Of all the 90 teleradium-treated patients 22 = 24 % survived for 3 years and 11 = 12 % survived for more than 5 years, while the corresponding figures for those receiving only roentgen treatment are only 13 % and 1.4 % respectively.

Thus we find a verified difference, and while the average age of the patients in the 1st group proves to be 66 years and in the 2nd and 3rd group 65.7 years we cannot explain the difference hereby. Nor are the roentgenologically treated cases more advanced. Among the 82 patients with skeletal metastases 39 are to be found in the 1st group and the rest in the 2nd and 3rd. This little difference cannot have had any influence on the figures to speak of.

The explanation of the proved difference in the results of treatment between the patients who only were irradiated with roentgen rays and those who were treated with teleradium I think we above all had to look for in the facts that by use of the latter method as a rule *an increased dose* had been given in the prostatic region. The total tumour dose had generally been about 500—1,000 r higher because of the additional dose from the perineal field. Among the 70 roentgen-treated patients only 30 had received any irradiation from perineum and usually small doses about 900—1,200 r, during the later years up to 1,500 r. Thus not even half of these patients had got as large a dose as those treated with teleradium.

In some of the cases irradiated with teleradium I think *we cannot exclude the possibility of a castration* in spite of the careful protection of the testicles during the irradiation. 32 patients had got 3,600—4,500 r from the perineal field and measurements performed by Dr. phil. SVEN BENNER from our Radiophysical Institute have proved that by these doses we must count with a dose in the testicles of about 350—500 r

even when they were protected with a filter of 6 mm Pb equivalence. — Of these 32 cases only 5 died within 1 year and 12 within 1—2 years, while 5 survived for 5 years and 10 lived 2—5 years after the treatment. — Perhaps it is possible that the better result by the patients irradiated with teleradium to a certain extent depends upon the hereby caused unintentional castration.

Of all the 167 patients 6 died of intercurrent diseases.

I have also investigated the *average length of survival in months* for the 105 patients who either had metastases on admittance or got them developed in the sequel, counting *from the point of time when their metastases were observed*. The calculated mean period of survival I have found to be *12.9 months*. By way of comparison it may be mentioned that of BUMPUS's material of 1,000 cases $^2/_3$ died within 9 months after the observation of metastases, while NESBIT & CUMMINGS report an average survival of 11.3 months after castration in a material of 75 cases, while ROMANUS states a corresponding figure of 13 months for 17 patients who were castrated by operation.

This survey of Radiumhemmet's material of cancer of the prostate has thus shown that with only radiation treatment we have been able to afford considerable help to those suffering from this complaint. — In *our present therapy*, where we endeavour to give *as big a dose as possible* towards the prostatic region *in one series* and then as a rule with roentgen radiation from 2 anterior and 2 posterior fields, as well as teleradium from the perineum, we use as auxiliary treatment both castration and estrogenic hormone therapy, and hope thus to be able to improve our results still further.

SUMMARY

The author has brought together Radiumhemmet's material of irradiated cancer of the prostate during the period 1929—1940. Of the 167 patients 107 were inoperable and these were treated with irradiation only. In 46 cases, of which 15 were radically operated upon, post-operative radiation therapy was given. 14 patients with local recurrences or metastases after an earlier operation were irradiated. The author lays stress upon that the operation to a great extent is performed by the perineal route, because it gives a better approach and increases the possibility of recognizing smaller carcinomas during the operation. Of the inoperable patients 16 % survived for more than 3 and $5^1/_2$ % for more than 5 years, and of all those operated upon 38 % survived for more than 3 and 20 % for more than 5 years.

No deliberate castration was undertaken. 70 patients got roentgen treatment only, 25 telecurietherapy and 65 a combination of both. Of the former 70 cases 13 % survived for more than 3 and 1.4 % for more than 5 years, and of all the 90 treated with teleradium 24 % survived for more than 3 and 12 % for more than 5 years.

The average length of survival of those patients who either had metastases already on admittance or got them developed in the sequel (105 cases together) was 12.9 months from the point of time when their metastases were observed.

ZUSAMMENFASSUNG

Verf. hat das Material des Radiumheims an bestrahlten Prostatakrebsen aus der Zeitspanne 1929—1940 zusammengebracht. Von den 167 Kranken waren 107 inoperabel, und diese sind nur mit Bestrahlung behandelt worden. 46 Fälle hatten postoperative Strahlenbehandlung bekommen, darunter 15 Radikaloperierte. 14 Kranke mit lokalem Rezidiv oder Metastasen nach einer früheren Operation sind gleichfalls bestrahlt worden. Verf. legt Gewicht darauf, dass die Operation in grossem Ausmasse auf perinealem Wege vorgenommen wird, da dieser besseren Zugang gewährt und grössere Möglichkeiten gibt, kleinere Karzinome während der Operation zu erkennen. Von den inoperablen Patienten überlebten 16 % mehr als 3 Jahre und 5½ % mehr als 5 Jahre. Von den operierten Fällen überlebten 38 % mehr als 3 Jahre und 20 % mehr als 5 Jahre nach der Operation.

Es wurde keine absichtliche Kastration vorgenommen. 70 Kranke bekamen nur Röntgenbehandlung, 25 Telecurietherapie und 65 eine Kombination von beiden. Von den erstgenannten 70 Fällen überlebten 13 % mehr als 3 und 1,4 % mehr als 5 Jahre, und von sämtlichen 90 mit Teleradium behandelten überlebten 24 % mehr als 3 Jahre und 12 % mehr als 5 Jahre.

Die durchschnittliche Überlebungsdauer derjenigen Kranken, die bei der Aufnahme bereits Metastasen hatten oder später solche bekamen (im ganzen 105 Fälle) betrug 12,9 Monate von dem Zeitpunkt an, wo ihre Metastasen entdeckt wurden.

RÉSUMÉ

L'auteur a collationné le matériel de cancers de la prostate irradiés à Radiumhemmet de 1929 à 1940. Sur les 167 malades 107 étaient inopérables et furent traités uniquement par irradiation. 46 cas avaient été admis pour actinothérapie postopératoire, 15 d'entre eux ayant subi une intervention radicale. 14 malades avec des récidives locales ou des métastases après une opération antérieure furent aussi irradiés. L'auteur insiste pour que l'opération soit généralement pratiquée par la voie périnéale parce que celle-ci donne un meilleur accès et augmente les possibilités de reconnaître les carcinomes de petites dimensions pendant l'intervention. Des malades inopérables 16 % survécurent plus de 3 ans et 5½ % plus de 5 ans. Des cas opérés 38 % survécurent plus de 3 et 20 % plus de 5 ans.

Aucune castration ne fut entreprise de propos délibéré. 70 malades ont reçu un traitement par les Rayons Roentgen seuls, 25 ont été soumis à la télécuriethérapie, et 65 à une combinaison des deux méthodes. Des 70 sujets du premier groupe 13 % étaient en vie après plus de 3 ans et 1.4 % après plus de 5 ans, et sur le total des 90 sujets traités par le téléradium 24 % survécurent plus de 3 ans et 12 % plus de 5.

La survie moyenne des malades qui ou bien avaient déjà des métastases à leur admission ou bien les virent se développer par la suite (105 en tout) a été de 12.9 mois à partir du moment ou ces métastases furent observées.

FROM THE RADIUMHEMMET, STOCKHOLM (CHIEF: PROFESSOR ELIS BERVEN)

A CASE OF CANCER OF THE OESOPHAGUS, ALIVE AND FREE FROM EVIDENCE OF TUMOUR 6 YEARS AFTER ROENTGEN TREATMENT[1]

by

Folke Jacobsson

The treatment of cancer in the thoracic part of the oesophagus still gives poor results. It appears from the literature that healing for 5 years or more after roentgen treatment is very rarely reported. BAUM in 1936 described a case of squamous cell carcinoma in the lower part of the oesophagus, involving the cardia, in which the patient was free from symptoms 6 years after the treatment. In 1937 HILTON reported a case of tumour in the middle part of the oesophagus. Biopsy was performed but there was, however, no histological verification in this case. According to a personal communication to SMITHERS in 1940 the patient in question had been free from symptoms for about 6 years. In 1943 SMITHERS had in his material a case of tumour in the middle part of the oesophagus, in which the patient was alive and free from symptoms 5 years after the treatment. The patient was aged 64 at the beginning of the treatment and received an estimated tumour dose of 6.300—6.900 r over 39 days. There was no histological verification in this case. There is also a case published by PALUGYAY which was not treated solely with roentgen but also locally with radium. The tumour was situated in the lower part of the oesophagus. The patient had lived for 8 years after the treatment but there was no histological verification of the tumour. The same combination of treatment was, according to STRANDQVIST (personal communication 1945), used in a case of squamous cell carcinoma. In this case the patient was living in a good condition 8 years after the treatment, but had a stenosis at the site of the tumour. Furthermore, some cases are described, in which the localization in the oesophagus is not indicated and no information is given about the histological diagnosis. Thus

[1] Submitted for publication, Jan. 9, 1946.

STEWARD (according to ADAM) treated two patients which lived free from signs and symptoms for more than 5 years, and DE SANTI (according to FINZI) one patient who lived for 10 years and afterwards died of liver metastases.

It would be valuable if every case of cancer of the thoracic part of the oesophagus, in which the patient has lived for more than 5 years, was described with particulars regarding the treatment and sequelae, especially injuries possibly caused by the treatment. A survey of such cases from the literature would then render it possible to elicit certain factors of importance for the continued improvement of the treatment.

One of the patients treated at the Radiumhemmet for cancer of the oesophagus has been alive and free from evidence of tumour more than 6 years after the treatment. The case is included in STRANDQVIST's series, published in 1941. The patient had then lived for two years after the treatment. This case will now be reported in its entirety.

Patient F. F. Record No. 2194/39. By occupation a waiter. He was 58 years of age, when he first was admitted to the Radiumhemmet in 1939. He had no known hereditary predisposition for cancer and had previously always been in good health.

Since about one year he had noticed, that on swallowing the food sometimes stuck rather far down in the gullet. Moreover, he periodically had pains in the chest, radiating towards the sternum and out towards the middle of the back. The patient consulted a doctor, who prescribed alkaline water. After the lapse of more than six months, roentgen examination revealed a tumour in the oesophagus, and the patient was sent for roentgen treatment. Though his appetite had been good throughout, the patient had lost 10 kg in weight. Latterly he had felt tired and languid, but had nevertheless been able to work. Since youth he had been a great smoker and had used alcohol regularly.

Status on the 1st of February 1939: General condition unaffected. Rather emaciated. No metastatic lymphatic nodes were palpable in the neck.

Roentgen examination revealed within the lower part of the oesophagus above the diaphragm a tumour about 5 cm in length, which did not involve the stomach. The opaque meal passed without difficulty (Fig. 1 a).

Oesophagoscopy revealed 34 cm from the teeth a circularly growing, easily bleeding, ulcerated tumour. Biopsy was performed and the pathological report of the biopsy specimen was squamous cell carcinoma with low differentiation.

The electrocardiogram was normal and roentgen examination of the lungs negative. The sedimentation test, according to the method of Westergren, 5 mm. The haemoglobin, according to the method of Hellige, 82 %, red cells 4,700,000 and white cells 6,400. The Wasserman reaction in the blood negative.

Roentgen treatment was given according to the method described by STRANDQVIST as cross-fire radiation from 3 anterior and 3 posterior fields. (The appearance of the anterior fields is shown by Fig. 4). The patient received altogether 3,600 r per field, except on the posterior central field and the left anterior lateral field each of which received 3,400 r. The treatment was given with about 175 kv and an intensity of about 50 r per minute, measured on the surface of the skin. As a filter $^1/_2$ mm Cu + 1 mm Al was used. The size of the fields was about 6 × 13 cm. The scheme of the treatment, taken from STRANDQVIST's article, is shown by Fig. 2. (The skin dosages include backscatter.)

The tumour dosage was estimated at about 5,000 r over 35 days.

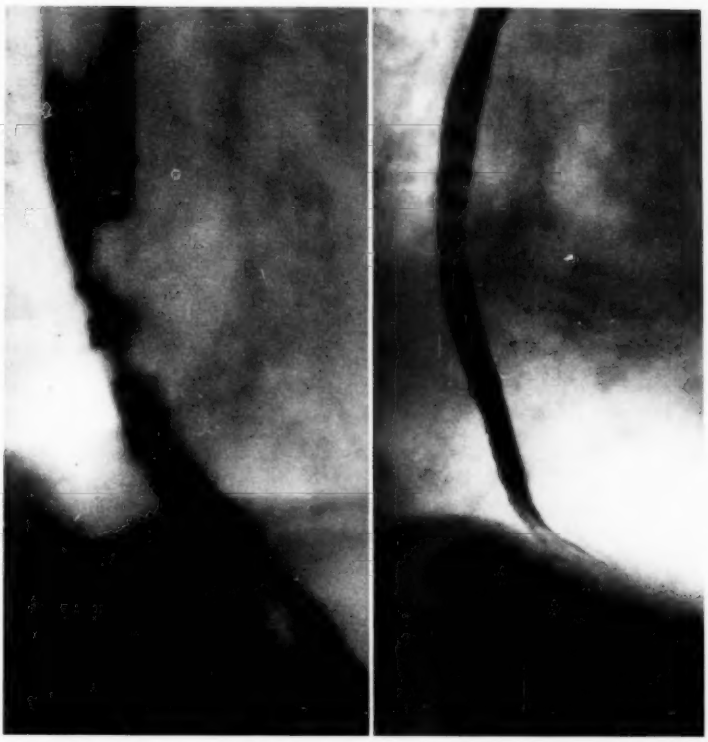

Fig. 1 a. Oesophagus before the treatment.

Fig. 1 b. Six years later.

The patient took the treatment well, had throughout it a normal temperature and his weight was maintained unchanged. He found it easier to swallow and, on discharge from the hospital, was able to eat all kinds of food. As a reaction on the skin, a blistering epidermitis developed.

On roentgen control of the oesophagus two months after the treatment, the opaque meal passed freely, and no infiltration of the wall coul l be roentgenologically observed. Since then the roentgen findings in the oesophagus have remained negative.

3 months after the treatment the patient had slight hacking cough and a stitch to the right of the chest. Roentgen examination of the lungs showed a small induration in the right lung on a level with the tumour. This induration, on control after the lapse of 3 months, still remained, but had cleared after 9 months and was interpreted as a radiation reaction.

One year after the treatment the patient's general condition was satisfactory. He had a good appetite and had recovered his lost weight, but now and then had a slight dull pain in the middle of the chest as well as a hacking cough. Considerable skin changes

Day No	Field No.	Skin dose per treatment	Tumour dose per day	Day No.	Field No.	Skin dose per treatment	Tumour dose per day
1	II	800 r	215 r	19	II	600 r	165 r
2	V	800	215	20	I	600	130
3	VI	800	175				3,695
4	I	800	175				
5	III, IV	800, 800	355	21	III	600	130
				22	—	—	—
6	II	800	215	23	VI	600	130
7	I, VI	800, 800	355	24	—	—	—
8	V	800	215	25	V	600	165
9	III	800	175	26	IV	600	130
10	—	—	—	27	I	400	90
			2,095	28	II	400	110
				29	III	400	90
11	IV	800	175	30	VI	400	90
							4,630
12	II	800	215	31	—	—	—
13	I	800	175	32	V	400	110
14	III	800	175	33	IV	400	90
15	VI	800	175	34	I, VI	200, 200	90
16	V	800	215	35	II, IV	200, 200	100
17	—	—	—				
18	IV	800	175		A total of	21,200 r	5,020 r

Field I	3,600 r
» II	3,600
» III	3,400
» IV	3,600
» V	3,400
» VI	3,600

Fig. 2. Scheme of the dosage in the treatment of the case.

were observed: The anterior fields showed small plications as well as distinct induration. The skin was tightened over the sternum. The changes were most marked on the posterior fields. In the central field there was a large oedema cushion, so that it looked as if the patient had a gibbus.

A moderate enlargement of the heart was roentgenologically found 3 months after the treatment and had considerably increased one year afterwards. Since then it has been stationary. Fig. 3 shows the heart before the treatment and 1 year later. In the electrocardiogram minor changes were detectable within 3 months after the treatment. After 2 years the electrocardiogram was unchanged but after the lapse of $5^1/_2$ years it had changed and showed signs of probable intraventricular conduction disturbances. As the roentgen examination of the heart and the electrocardiogram were normal before the treatment and as the heart owing to the position of the tumour, which lay behind it, was brought into the radiation area, the heart lesions were regarded as probably due to the treatment.

Three years after the treatment an exudate developed in the right pleura. The patient felt tired and easily got out of breath. 800 cc of the exudate was drawn out by suction. The patient felt better, but after about half a year again became very short of breath. Roentgen examination showed that the exudate had again increased and 700 cc was again drawn out by suction. The exudate was examined for tumour cells with a negative result. The sedimentation test was 43 mm. The patient again improved.

His condition since then has been maintained on the whole satisfactory. He has no difficulty in swallowing, but now and then a slight hacking cough and gets breathless when walking uphill, but not on flat ground. Moreover, he feels dull pain in the middle of the chest on exertion. His capacity for work is reduced about as much as might have been expected from the heart lesion and the pleura exudate. The patient has no manifest

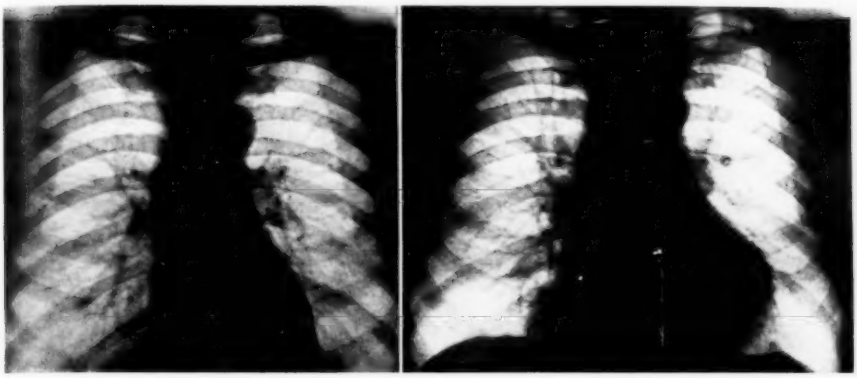

Fig. 3 a. The heart before the treatment. Fig. 3 b. One year later.

heart insufficiency and does not require cardiacs. Roentgenologically, there was no essential change of the pleural exudate by examination more than 6 years after the treatment as compared with the status $2^1/_2$ years earlier, except that the exudate during this period had been partly organized. A renewed examination for tumour cells in the exudate was then made but this time too with a negative result.

The appearance of the patient 6 years after the treatment is shown by Fig. 4, and the status of the oesophagus by Fig. 1 b. On the fields an abundance of teleangiectases and a considerable atrophy of the skin were observed. On the two central fields the skin looks as if it were glued to the underlying tissues. On the lateral fields the skin is not quite fixed. — Blood examination showed haemoglobin, according to HELLIGE, 80 %, red cells 4.02 millions and white cells 5,800. Sedimentation test 20 mm.

The only oesophagoscopy after the treatment was made $5^1/_2$ years later. The mucous membrane was then throughout soft and normal, without any signs of a tumour. Even for a trained observer it was difficult to see where the tumour had been.

It was thus the case of a man aged 58 with a low-differentiated squamous cell carcinoma in the lower part of the oesophagus, with a one-year history. He received roentgen treatment with a tumour dosage estimated at about 5,000 r over 35 days. 2 months after the treatment he was subjectively and objectively free from signs and symptoms. More than 6 years after the treatment he is still cured locally, without difficulties in swallowing and without noticeable metastases. However, he is not fully capable of work in his occupation as a waiter as he is liable to get short of breath and has pain in the middle of the chest on exertion. These symptoms were regarded as due to a cardiac lesion, which had arisen after the treatment, and a pleura exudate which had supervened.

The heart lesion was regarded as probably due to the treatment, as the electrocardiogram and the heart roentgen had previously been

Fig. 4. The appearance of the patient and anterior fields 6 years after the treatment.

normal, and as the heart, owing to the position of the tumour, which was situated behind it, had been included in the radiation area.

Roentgenologically there was no essential change of the pleural exudate by examination more than 6 years after the treatment as compared with the status $2^1/_2$ years earlier, except that the exudate had partly been organized. Two examinations for the possible presence of tumour cells in the exudate were negative. In view of these facts, it seems not likely that pleural metastases exist and the exudate is probably likewise due to the treatment.

SUMMARY

Description of a case of low-differentiated squamous cell carcinoma in the lower part of the oesophagus with a one-year history. Roentgen treatment was given, with an estimated tumour dosage of about 5,000 r over 35 days. The patient has been alive and

free from evidence of tumour more than 6 years after the treatment. As a probable consequence of the radiation treatment, an enlargement of the heart and a pleural exudate with resulting moderate subjective symptoms ensued.

ZUSAMMENFASSUNG

Beschreibung eines Falles von niedrig differenziertem Plattenepithelkarzinom in der unteren Partie der Speiseröhre mit einjähriger Krankengeschichte. Es wurde Röntgenbehandlung gegeben, und zwar mit einer Tumordosis von schätzungsweise etwa 5,000 r im Laufe von 35 Tagen. Der Kranke ist mehr als 6 Jahre nach der Behandlung am Leben und frei von Tumorsymptomen. Wahrscheinlich als Folge der Bestrahlungsbehandlung traten eine Herzvergrösserung und ein Pleuraexsudat auf, mit daraus folgenden, mässigen subjektiven Symptomen.

RÉSUMÉ

Description d'un cas de cancer épithélial pavimenteux, faiblement différencié, localisé à la partie inférierure de l'oesophage et dont l'anamnèse remontait à une année. On institua un traitement par les rayons Roentgen, la dose tumorale étant, selon le calcul, d'environ 5,000 r en 35 jours. Le malade a vécu plus de 6 ans après le traitement sans signes de persistance de sa tumeur. On a vu apparaître, vraisemblablement à la suite de la radiothérapie, une hypertrophie du cœur et un épanchement pleural entraînant des troubles subjectifs modérés.

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FROM RADIUMHEMMET, STOCKHOLM (CHIEF: PROFESSOR ELIS BERVEN)

RESULTS OF RADIOTHERAPY OF EPIBULBAR TUMORS AT RADIUMHEMMET, STOCKHOLM, 1920—1940[1]

by

Harry Larsson

The term epibulbar tumor is used here to signify tumors appearing in the conjunctiva on the anterior side of the bulbus oculi. They are accessible to direct inspection and external treatment.

There are different clinical types, the most important one being the congenital, naevogenic tumors. Histologically, these are characterized by groups of naevus cells situated either under or within the epithelium. The cells vary in shape and size and have a comparatively large, dark-coloured nucleus. In some instances, the cells contain pigment showing negative iron reaction. This pigment may also lie outside the naevus cells, either freely in the connective tissue, or in the epithelial cells. In addition, unpigmented naevogenic tumors are to be met with.

Different theories have been advanced regarding the origin of the naevogenic tumors. v. RECKLINGHAUSEN considered them to have an endothelial origin. UNNA, among others, was of the opinion that they consist of epithelial cells which have been dislocated from the normal epithelium. RIBBERT stated that their origin was mesoblastic. According to MASSON's now almost generally accepted theory these tumors are neither epithelial nor mesoblastic, but of a neuro-ectodermal origin. All the transitions from the normal end organs of the nerves to the typical naevus cells can be seen.

The naevogenic tumors are to be found, partly in a benign form which is defined as pigmented naevus, and partly in a malignant form which is suitably referred to as malignant melanoma.

From a clinical point of view, a naevus is most often manifested in the form of a pigmented, sometimes multilocular tumor which in the majority of cases is localized close to the limbus. As a rule, it is superficial and can be displaced together with the conjunctiva towards the sclera. Its consistency is soft and the surface is even. In the surrounding parts, a

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strand of vessels is frequently found radiating towards the tumor. The tumor is sometimes cystic. The rate of growth varies, being generally slow.

In certain cases, it becomes malignant and growth is then accelerated. However, it is usually impossible to determine at an early stage, and merely by means of the clinical picture, whether it is a naevus in the process of rapid growth but still benign, or has actually become malignant. P. WÄTZOLD presented the following characteristics, according to which a naevus may be considered as benign, viz., slight extention (up to the size of a lentil), and slow growth. A naevus may be suspected of malignant degeneration when it has begun to grow more rapidly in a patient of more than 30 years of age. According to WÄTZOLD, definite malignancy is present when it has extended over the greater part of the bulb or — of course — when metastases occur.

As regards the epithelial tumors in the conjunctiva, the *papillomas* are of significance in this respect, owing to the fact that they have a tendency towards recurrence after surgical removal and, in certain cases, may develop into cancer. They sometimes appear in the form of pedunculated, reddish-grey, often rapidly growing tumors with a rough surface. These tumors are also often noticed close to the limbus. Histologically, they consist of a central strand of vessels and connective tissue which is covered by a sometimes strongly thickened stratified epithelium.

Cancer in the conjunctiva is, from a histological point of view, almost invariably a squamous cell carcinoma, but cases of basal cell cancer have also been described. The tumor may start as a papilloma which later becomes malignant. Its growth is at times slow, gradually extending over to the cornea and liable to ulcerations. However, haemorrhages are fairly rare. It appears in the form of a solid, greyish-white tumor with an irregular surface which is fixed to the substratum. Metastasis takes place rather late.

Fibromas originate in the connective tissue and form the most common polypous tumor of the conjunctiva. Its surface is even, contrary to the papillomas. As a rule, the fibromas are comparatively soft, have a rapid growth and easily bleed.

Primary, unpigmented conjunctival sarcomas are very rare.

Lipomas, dermoids, and lipodermoids are less common conjunctival tumors.

In this connection, the vascular tumors, among which the cavernous haemangiomas are most common, deserve special attention, as being sensitive to irradiation.

As chiefly cases of relatively radiosensitive tumors are referred to Radiumhemmet, some of the mentioned tumor forms are not represented in the material of this clinic.

Nowadays, the normal method of irradiation of the epibulbar tumors at Radiumhemmet consists of superficial application of radium.

The epibulbar tumors, the naevi, in particular, generally have but a slight thickness, and many are hardly noticeable above the surface. By means of superficial application of radium preparations with low filtration, large radiation doses can be given to the conjunctiva and the superficial parts of the sclera, while the deeper parts of the eye receives a considerably smaller dose. At the treatment, plane preparations are used, containing 10 and 5 mg of radium element, respectively. The radium sulphate is fused into a porcelain plate, and the rays are filtered through 0.2 mm of nickel or German silver. The preparations measure 1 × 1 and $^1/_2$ × 1 cm, respectively, and are denoted as C-plane 1 × 1 and C-plane $^1/_2$ × 1. In the case of larger tumors which are not covered by one single preparation, several preparations are placed close to each other, at an angle suited to the curve of the bulb. They are fixed to a handle by means of which they are held up against the tumor, as a rule, without previous anaesthesia of the conjunctiva. The preparation cannot in this way be pressed against the tumor, but nevertheless can be held quite close to it, and a mechanical irritation of the tumor may thus be avoided. Usually, 1 or 2 daily applications lasting half an hour each are made. The total period of treatment is adapted to the particular type of tumor and its size. In the case of small, superficial tumors, without a clinical suspicion of malignancy, 3—4 such treatments are administered, *i.e.* $1^1/_2$—2 hours in all. This cautious dosage does not, as a rule, cause the patient any subjective troubles, and the reaction in the tumor surroundings is hardly visible. On the other hand, a larger dose is given, when the tumors are more extensive or rise higher above the surface, by increasing the number of applications, generally to 6—8, but occasionally to 10—12. The patient then has subjective symptoms, such as a smarting pain and an increased flow of tears. The objective symptoms are redness, swelling, and at times a flow of tears. Several of these series are administered at intervals of 1—2 months, dependent on the degree of suspicion of malignancy and the rate of reaction to treatment on the part of the tumor.

In order to obtain a conception of the radiation doses given in this method of treatment, BENNER of the Radio-Physical Institution at Radiumhemmet has measured with a phantom chamber the absorption of the radiation of the C-plane in successive layers corresponding to a tissue depth of up to 2.8 mm. (See Table 1.) It has then been assumed, on the basis of earlier measurements, that the pure γ-radiation in the case of a C-plane 1 × 1, without additional filters will equal 16 per cent of the total ionisation intensity and, further, 1 Imc has been equalled to 8 r/hour. In this way, the following values of intensity of the middle point normal of the C-plane 1 × 1 are obtained.

Table 1

Irradiation of C-plane 1 × 1 in layers corresponding to a tissue depth of up to 2.8 mm.

Depth in mm	r/hour	
0	4,520	
0.2	4,040	
0.4	3,600	
0.6	3,360	
0.8	2,820	
1.0	2,460	
1.4	1,870	
1.8	1,400	
2.2	1,015	
2.8	560	At these depths, the β-radiation
5.0	152	from the preparation is assumed
10.0	59	to have been filtered away

As will be seen from this table, a very high intensity would be reached on the surface of the tumor if the preparation were pressed close to it. Owing to the fact that the plane preparation does not in all places lie close to the spherical bulb, and cannot, in addition, be pressed to the tumor since the conjunctiva is not anaesthetized, an intensity is in reality obtained in the region under treatment which is probably considerably lower than the calculated value. In conformity with this, but a slight radiation reaction is produced in the conjunctiva.

The table also shows that the intensity rapidly falls with increase of depth under the surface. Even at a depth of 2 mm it has decreased to approximately 30 per cent of the surface dose, and at 3 mm only about 10 per cent of the surface dose remains.

The size of the bulb varies according to age and refraction. In order to form an idea of the doses which reach the anterior and posterior surfaces, respectively, of the lens, 3—4 mm is stated as an approximate measure of the distance from the corneal top to the anterior surface of the lens, and 6—7 mm for that of the posterior surface. The distance from the limbus, where most of the epibulbar tumors are situated, to the nearest part of the posterior lens capsule also probably equals 3—4 mm. Thus, not more than a maximum of 10 per cent of the superficial dose reaches the lens at this form of treatment.

This method with superficial application of plane preparations has been employed in the majority of cases of epibulbar tumors at Radiumhemmet (*i.e.* 46 cases out of 66).

In the case of more elevated tumors, where the radium preparations with low filtration would have caused but a slight effect in the deeper parts of the tumor, implantation or superficial application of filtered

radium needles has been adopted. As regards the doses which may be adopted in this connection, reference is made to one of the cases in group III. In a few cases, also other radium preparations with a still heavier filtration have been employed. However, owing to the relatively greater depth dose, the risk of radiation damage to the lens is increased and these preparations have, consequently, only been used in exceptional cases.

In cases with clinical malignancy, roentgen treatment in large doses has been applied, in some instances combined with a short distance treatment with radium.

Teleradium for the primary tumor has only been used in a few cases. On the other hand, it has formed the normal method in treatment of suspected or definite lymph node metastases.

The material of irradiated epibulbar tumors at Radiumhemmet during the period of 1920—1940 comprises a total of 66 cases. These cases have been classified in the following way:

Group I.	Growing epibulbar tumors without definite clinical or microscopic evidence of malignancy	37
Group II.	Naevogenic tumors with suspicion of malignancy	7
Group III.	Malignant naevogenic tumors	14
Group IV.	Papillomas	2
Group V.	Carcinomas	6
		66

When an earlier stationary epibulbar tumor begins to grow, or when a slowly growing tumor of this type starts to grow rapidly, it is not always possible, as has been earlier mentioned, to determine by clinical means whether it is to be regarded as a still benign tumor, or has malignified.

It has been pointed out in several quarters (WÄTZOLD, SCHICKER, BRÜCKNER, among others) that a biopsy examination of epibulbar tumors is directly contraindicated owing to the risk of malignification and spread of the tumor. It should therefore be altogether excluded, or else replaced by a total extirpation of the tumor with a fair margin. The fact that in several cases in the history of patients, suffering from epibulbar tumors, the growth of the tumor has in their own opinion, begun with a trauma, points in the same direction. The trauma has, as a rule, been of a mechanical kind, *i.e.* in the form of a blow to the eye by, for instance, a branch of a tree, or a foreign body in the eye. In a few instances, the patient has been subjected to chemical irritation due to lime in the eye.

The table below presents the number of cases in which a trauma to the eyes has been reported in the history in the various groups of cases.

Cases of epibulbar tumors with a trauma to the eye

In group	I	.....	trauma in	3	cases out of	37
»	»	II	.....	»	»	2	»	»	»	7
»	»	III	.....	»	»	5	»	»	»	14
»	»	IV	.....	»	»	0	»	»	»	2
»	»	V	.....	»	»	2	»	»	»	6

Thus, a trauma occurs in the history in more than $^1/_3$ of the cases of malignant naevi. This speaks in favour of an emphatic warning against the form of trauma which may result from biopsy or incomplete extirpation of tumors. Accordingly, a patho-anatomical diagnosis is lacking in several of the cases, and the classification into various groups has, to a great extent, had to be performed on the basis of clinical observations.

Group I

Growing epibulbar tumors without histological or the above mentioned clinical signs of malignancy have been referred to group I. In this group have also been included the cases where histological examination is lacking but no clinical sign of malignancy has been found.

A patho-anatomical diagnosis is noted in only 6 of 37 cases. The boundary between this group and the rest is therefore vague and, in a few instances, the classification is uncertain.

The main indication for radiation treatment in group I is therefore the growing of the tumor no matter whether it will turn out a question of malignified tumor where the clinical signs of malignancy have not as yet had time to develop, or a growing benign tumor. Even stationary tumors have been treated, however, chiefly as a prophylactic measure, but to some extent also for cosmetical reasons.

In 29 of the cases in this group, superficial application of plane preparations has been adopted according to the normal method. The epibulbar naevi react to treatment in a few cases as soon as after a few weeks, but sometimes it will take several months before they begin to diminish. At times, the tumor as well as the pigmentation disappear completely, while in other instances a faint, yellowish colour remains. As a rule, the superficial, dilated vessels also remain which are often visible in the adjacent parts of the naevus.

Results of radiation treatment in group I

Num. of cases	S-free[1] 5 yrs	Tumor rest unchanged 5 yrs	Tumor rest operated within 5 yrs after treatment	Died within 5 yrs in intercurrent disease
37	30	5 incl. growth in 2 cases after 5 years	1	1

[1] S-free = symptomfree.

It will be seen from the table that 30 of the 37 irradiated cases became completely free from symptoms after treatment. Of these 30 patients 12 were observed during more than 15 years. A tumor rest remained in 5 cases after the treatment, which had in all these cases remained unchanged for more than 5 years. However, growth of the tumor rest took place later in 2 of the cases.

In one of these 2 cases the tumor rest began to grow 7 years after the treatment. The treatment had been administered with 1 C-plane $^1/_2 \times 1$ for $4^1/_2$ hours in all. Enucleation was performed since the tumor was growing into the cornea. The histologic examination showed strongly pigmented naevus without indications of malignancy.

The other case was treated with a fairly large dose, viz., 1 C-plane $^1/_2 \times 1$ for 8 hours in all. The tumor rest remained, and began to grow after approx. 12 years. Further treatment was then given with 2 C-planes $^1/_2 \times 1$ for 2 hours. At a control examination 3 years after the last treatment, no clouding in the media was observed. The tumor was somewhat smaller at that time. Owing to pains in the eye, an operation was suggested to the patient but this has not yet been performed.

The case which was operated upon within 5 years after the treatment owing to a remaining tumor rest, was subjected to this intervention since the tumor appeared to be but slightly sensitive to irradiation. However, no growth had occurred. In addition, an enlarged lymph node was noticed which was suspected of metastasis. P-A-D-cystic naevus without malignancy. The patient died 12 years later of cancer of the prostate.

Furthermore, a patient in group I died three years after the treatment in an intercurrent disease without signs of recurrence.

Conclusion: Growing naevi should, apparently first be subjected to irradiation without a previous biopsy examination. They should then be followed by careful control examinations. If growth is observed, operation should not immediately be resorted to. Instead, renewed irradiation. This is regarded as prae-operative treatment. When the reaction is over, surgical intervention may take place though as a rule as conservatively as possible. If the patho-anatomical diagnosis reveals a malignant tumor, a more extensive operation should be carried out.

Group II

Naevogenic tumors with suspected malignancy according to the patho-anatomical diagnosis.

Only the cases where the patho-anatomical examination has disclosed a suspicion of malignancy have been included in this group. All the 7 cases have been treated with superficial application of radium.

Results of treatment in group II

Num. of cases	S-free for 5 years		Op. tumor rest with recurrence later
7	6		1
	incl. post-op. tr.	incl. prae-op. tr.	
	5	1	

In five of the cases, extirpation of the tumor had been carried out before treatment. In one of these cases it had taken place 13 years earlier, and a small local recurrence or new naevus was now noticeable. Approx. 1,500 r were given to the surface of the tumor. However, it did not disappear completely and was therefore extirpated. P-A-D: cellular naevus, malignancy not altogether excluded. Still free from symptoms 15 years after the treatment.

In the other four cases operated upon before the irradiation, no remaining tumor was seen and the radiotherapy was given as a prophylactic measure. All the cases were free from recurrence for 10 years. P-A-D: All four cases disclosed a naevus with suspicion of malignancy.

In one of the cases not operated upon before treatment, a distinct regression was noted, but a tumor rest remained. This was removed by surgery after 2 years, at the patient's own request. P-A-D: Naevus, exclusion of malignancy impossible. In the second case not operated upon primarily, no decrease of the tumor was obtained after treatment (1 C-plane 1 × 1 for 4 hours). Accordingly, it was excised by means of electro-endothermy. P-A-D: Naevus with suspected malignancy. The patient has been subjected to repeated recurrences which have been excised by means of electro-endothermy 7—8 times. No further irradiation.

Conclusion: Group II cannot be clinically differentiated from group I. The treatment is planned and performed as in group I. If a tumor rest remains, new treatment is administered, which is regarded as prae-operative treatment. If no rapid regression takes place then, operation is resorted to and carried out as conservatively as possible. If the patho-anatomical diagnosis causes suspicion of malignancy, the patient is subjected to frequent follow up examinations. In the event of recurrence, extensive operation must be taken into consideration. Should the patho-anatomical diagnosis show definite malignancy, radical intervention is performed either immediately or after prae-operative irradiation.

Group III

Malignant naevogenic tumor.

In this group, 14 cases have been compiled where the histologic examination showed malignant naevogenic tumors, or the clinical course disclosed definite malignancy.

Definite malignancy acc. P-A-D.	10 cases
Suspected malignancy acc. P-A-D but clinically definite malignancy	2 cases
Clinically definite malignancy but without P-A-D.	2 cases

Apart from the 10 cases of definite malignancy according to the histologic examination, this group also includes two cases with suspected malignancy according to the patho-anatomical diagnosis, where however the continued course revealed definite clinical malignancy in the form of metastases. Furthermore, there are two cases without a patho-anatomical diagnosis but where the clinical course showed definite malignancy.

In twelve of the cases, operation had been performed before the irra-

diation, and in five of them, one or several instances of recurrence had undergone surgical intervention before introducing radiological treatment.

Table of the results of treatment in group III

Num. of cases	Free from symptoms for 5 years			Died of the tumor within 5 yrs	Died of other disease within 5 yrs (locally free from symptoms)
14	7			6	1
	Op. + post-op. tr.	Prae-op. tr. + op.	Only irradiation		
	5	1	1		

5 of the 7 cases which had been free from symptoms for more than 5 years after the treatment had been operated upon before the irradiation.

One of them had been subjected to evisceration almost a month prior to the treatment owing to the recurrence of the tumor after extirpation almost 2 months before the evisceration. In this case, roentgen treatment was given to the orbit with 2,400 r against a frontal field and 1,600 r against a lateral field. P-A-D: malignant melanoma.

In the second case, a tumor rest remained after the operation, which had begun to grow during the last year. Treated with 1 C-plane $^1/_2 \times 1$ for a total of $6^1/_2$ hours distributed among 5 series during approx. 1 year. In addition, further treatment with other radium preparations. The tumor diminished considerably, but a rest remained. It began to grow again 3 years after the beginning of the treatment. Then, further treatment was administered with 1 C-plane $^1/_2 \times 1$ for $2^1/_2$ hours in all and the tumor completely disappeared. It again began to grow after 2 years. Enucleation was performed and the patient has since been free from symptoms for 7 years. P-A-D: naevogenic tumor with sarcoma-like structures.

In the third case, the tumor had been extirpated approx. 3 weeks before the irradiation. Acc. to the P-A-D, which disclosed a malignant naevus, the radicality was questionable, but no tumor rest was seen macroscopically. Treatment was administered with 1 C-plane $^1/_2 \times 1$ for a total of $3^1/_2$ hours. The patient has since been free from symptoms for 7 years.

The fourth of the cases which had been free from symptoms for more than 5 years after the total extirpation + post-operative treatment was subjected to roentgen treatment in large doses on the eye (almost 1,800 r). Still free from recurrence after 13 years. Three years after the treatment a posterior corticalis cataract was noticed on the treated eye (see below, radiation injuries).

Finally, this group includes a case of malignant naevus where local radiation treatment was refused since the tumor was considered too extensive. Coagulation of the tumor itself was performed instead, since it could be carried out without injuring the eye (P-A-D: malignant naevus). Approx. $1^1/_2$ year later, the patient got a submandibular metastasis on the operated side. No prae-auricular gland was felt. Roentgen treatment was given on a large region comprising the right side of the neck and extending upwards prae-auricularly. Dose approx. 1,250 r, $^1/_2$ Cu, 40 cm distance. Approx. 3 weeks later, a lymph node was removed in the right fossa submaxillaris and radium was introduced into the operation cavity (960 mg/hour). P-A-D of the gland was metastasis of malignant naevogenic tumor. The patient has been free from symptoms at repeated control examinations, ever since as regards the eye which had never been subjected to radiation treatment,

and for 8 years as regards the glandular region. After this period of time, she obtained an extensive tumor growth on the cheek round the eye, as well as in the glands submentally and died a few months later without having been given further radiation treatment.

The case which was first subjected to irradiation and then operated upon was given 1 C-plane 1 × 1 for 1 1/2 hour in all. Owing to continued growth of the tumor at the edge of the field of treatment, implantation was later performed with 1 needle containing 5 mg of radium element for 4 hours (approx. calculated at 1,200 r, 5 mm from the middle-point of the needle). Since the tumor did not disappear in spite of this treatment, teleradium was given about 1/2 year later in 2 fields to the orbit with a total of 4,800 r per field. Approx. 2 months later, the patient showed signs of a glaucoma in this eye. Consequently, enucleation was performed. P-A-D: malignant melanoma. Then another 2 post-op. teleradium series were administered to the orbit. The patient died 11 years afterwards from a cerebral haemorrhage without any local recurrence or metastases (see below regarding radiation injuries).

The pat. who had been free from symptoms for more than 5 years after merely radiation treatment had been subjected to a biopsy examination before being admitted to Radiumhemmet. P-A-D: malignant tumor, mostly of a naevogenic nature. Since the tumor was considered to be too elevated to admit a sufficient dose into its base by means of the usual treatment, 5 needles containing 10 mg of radium element were fixed to a handle which was held up against the tumor for a total of 4 hours. According to calculations by BENNER, this gave a maximal surface dose of approx. 13,500 r. At a dose of a depth of 2 mm, 6,400 r were calculated at the centre of the middle needle, and at the end of the salt pillar in the outer needles 4,000 r. The tumor disappeared and the pat. is still free from symptoms. According to the patient's own report, vision has not deteriorated on the treated eye.

All 6 patients which have died of the basal disease within 5 years after the beginning of the treatment had been operated upon before this treatment. The first 4 patients had been subjected to recurrence after the operation at the beginning of the irradiation. The last 2 cases were admitted for prophylactic post-operative irradiation comparatively soon after the surgical intervention.

In this group, 2 cases have been included where the patho-anatomical diagnosis is lacking. The patients had both had pigmented tumors in the conjunctiva which had recidivated repeatedly in spite of operation and irradiation. They finally died of metastases.

A third case showed a tumor which had recidivated repeatedly after operation. 2 needles containing 5 mg of radium element had been implanted for 7 hours. The patient became free from symptoms locally but died three years later of metastases. P-A-D: melanosarcoma.

In the fourth case, where the tumor was extirpated a few weeks prior to treatment, a roentgen treatment was given to the eye for prophylactic purposes with 1,600 r. P-A-D: malignant melanoma. After 2 years, local recurrence and the patient died shortly afterwards of pulmonary metastases.

The tumor had been extirpated, in the fifth case, approx. a forthnight prior to treatment. P-A-D: naevus with *suspected* malignancy. Treated with 1 C-plane of 1/2 × 1 for 4 hours in all. Half a year later, a new small melanoma appeared in another spot in the conjunctiva. Treatment with 1 C-plane of 1/2 × 1 for 1 1/2 hour. After this, the new melanoma was extirpated (P-A-D: as before, naevus with suspected malignancy). A few months later, metastases which progressed in spite of teleradium treatment.

In the last case in this group, the tumor had been partly extirpated approx. 2 years previously. The tumor rest had at first remained unchanged but had begun to grow later. Radium treatment was given with 1 C-plane of $^1/_2 \times 1$ for 3 hours. A couple of months later, a metastasis appeared in the submandibular region. It was treated with roentgen (approx. 1,500 r). The tumor on the eye remained unchanged, but when the metastasis increased, intubation was performed with radium needles (in all 79 mg for 8 hours) and 2 months later, the gland was extirpated under local anaesthesia, during which process 47 mg of radium element were introduced into the wound cavity for 15 hours. P-A-D: melanosarcoma. When the tumor on the eye had failed to decrease, it was extirpated approx. 4 months after the treatment (P-A-D: melanoma with *suspected* malignancy). After a few months, the patient was subjected to further metastases and died approx. $1^1/_2$ year after the first treatment.

Finally, a case belongs to group III which died of an intercurrent disease within 5 years after the treatment without any signs of recurrence. Two months prior to the irradiation, a stalked tumor, the size of a hazel-nut, was extirpated. P-A-D: melanoma malign. At the beginning of the treatment, a brown pigmentation of almost the entire conjunctiva occurred and, in addition, a metastasis, the size of an almond, pre-auricularly. Teleradium treatment was introduced, and it was intended from the very start to evacuate the orbit as well as the glandular region after the radiation treatment. Therefore, regard need not be paid to the radiation injury of the eye. Teleradium treatment was administered in a field straight to the eye (30 gr-hours with a 5 gr teleradium apparatus and in a prae-auricular field 35 gr-hours, and in a submandibular field 20 gr-hours). Approx. a fortnight later, evisceratio orbitae was performed, including also excision of the greater part of the eyelid. P-A-D: melanoma malign. After another fortnight, the prae-auricular lymph node was extirpated (P-A-D: malignant melanoma). Approx. 3 months later, a further 15 gr-hours of teleradium was given in the two glandular fields, owing to a suspicion of metastasis. The suspected lymph node metastasis disappeared and the patient lived afterwards without any local recurrence or new metastases for 4 years, after which time she died of a cardiac disease.

The few cases in this group do not permit of any definite conclusion as regards therapy. The results, with approximately half the number of cases healed, appear, nevertheless, amenable to improvement, in view of the results in groups I and II, provided the radiation treatment is given before the operation. If the tumor does not disappear, operation is taken into consideration, possibly, after renewed prae-operative irradiation.

Group IV

This group includes two cases of papilloma with suspected malignancy.

One of the cases revealed in the P-A-D a papilloma with suspected malignancy. It was treated with 1 C-plane of $^1/_2 \times 1$ for 2 hours. The tumor disappeared and the pat. was free from recurrence for $5^1/_2$ years, until he died of pneumonia.

The other case revealed papillomatous, stratified epithelial vegetations of a prae-cancerous type. Treatment with 1 C-plane of $^1/_2 \times 1$ for a total of 3 hours. Became temporarily free from symptoms but, after 4 years, was subjected to leucoplakia-like changes in the conjunctiva which were repeatedly scraped away during the years 1934—44. No further irradiation.

Therapy: At unpigmented, small epibulbar tumors without signs of clinical malignancy, the same procedure as in group I is adopted.

Group V

This group comprises 6 cases with a patho-anatomical diagnosis of cancer. They are as a rule easily distinguishable, from a clinical point of view, from the malignant melanomas.

Num. of cases	Free from symptoms for more than 5 years			Died within 5 years in conn. with op.	Died within 5 years of other disease
6	4			1	1
	Op. + post-op. tr.	Only irradiation	Irradiation + op.		
	1	1	2		

In the case given post-operative treatment, the P-A-D showed a squamous cell carcinoma. Treatment was administered a week after the extirpation of the tumor with 1 C-plane of 1 × 1 for 3 hours in all. The pat. has now been free from symptoms for 5 years.

The pat. who was given only radiation treatment had a large tumor which filled the entire orbit and covered the eye. He had been blind on this eye ever since the age of13—14 owing to a wound on the cornea. Since no regard need be paid in this case to the possibility of injuring the eye with the rays, roentgen was administered in large doses. On a frontal field towards the eye approx. 4,800 r were given and on a lateral field approx. 1,500 r. Biopsy examination of the tumor prior to treatment disclosed stratified epithelial cancer. The tumor disappeared and the pat. has been free from symptoms for approx. 10 years.

One of the two cases subjected to irradiation and then operated upon was treated with teleradium in large doses. P-A-D: squamous cell carcinoma. The tumor disappeared, but after a few months a small local recurrence was noted which was treated by placing 3 needles containing 10 mg of radium element against the tumor.

The tumor disappeared but a new recurrence occurred after $^3/_4$ of a year which was implanted with 4 needles containing 10 mg of radium element for 4 hours. When, this notwithstanding, a tumor rest remained, the orbit was evacuated and a remaining focus of squamous cell carcinoma, the size of a pea, was found at the histologic examination. Now free from symptoms for 13 years.

The other case was given roentgen treatment in a rather small dose (approx. 1,400 r). P-A-D: squamous cell carcinoma. When the tumor, after a temporary regression, again began to grow, enucleation was performed. The pat. free from recurrence for 23 years.

A case of recurrence after the extirpation of a tumor one year before, where the patho-anatomical diagnosis revealed a squamous cell papilloma-like hyperplasia, has been referred to the sub-division of deaths within 5 years after treatment in connection with operation. Treatment as soon as the recurrence was discovered with 2 C-planes of $^1/_2$ × 1 for 3 hours. Since the tumor continued to grow, enucleation was carried out 2 months after the treatment. The patient died of meningitis in connection with this operation. P-A-D: squamous cell carcinoma in the autoptic preparation.

A patient, belonging to group V has died of another disease within 5 years after the treatment. Approx. 2 months after the biopsy examination which revealed squamous cell carcinoma the patient was treated with implantation of 2 needles containing 5 mg of radium element for 5 hours. The patient died $^1/_2$ year later of pneumonia, still free from symptoms in the eye.

As regards the therapy, the same procedure as in group III.

Injuries to the eye have not been altogether avoidable at radiation treatment of the epibulbar tumors. In 5 cases, remaining ocular lesions are noticeable which may be due to the irradiation.

	Superficial application of plane preparations acc. normal method	Other form of short distance treatm. with radium	Teleradium	Roentgen
Num. of cases.....	1	1	1	2

The case which had been subjected to a radiation injury owing to the superficial application of a plane preparation according to the normal method concerned a girl of 1 year of age. She had a naevus, the size of half a pea, close to the limbus corneae which appeared to extend into the cornea. It was treated with 1 C-plane of $^1/_2 \times 1$ for 2 hours in all, *i.e.* a relatively small dose. After this treatment a slight local swelling and redness was seen which disappeared within approximately $1^1/_2$ month. The tumor gradually disappeared. Approximately six years after the treatment, a slight clouding was noticed in the temporal part of the cornea corresponding to the area of treatment. According to the ophthalmologist, no tumor rest occurred, but a diffuse clouding in the deep corneal layers which was, in his opinion, due to the radiation treatment. At a control at Radiumhemmet 4 years later, apparently unchanged condition. No information regarding deteriorated vision.

The other case of injury owing to short distance treatment with radium had not been subjected to superficial application in the usual manner. This was also a case of a child, 10 months old, who was strongly suspected of having an epibulbar malignant melanoma. The clinical examination revealed a blackish-blue tumor in the superior fornix, extending along the greater part of the fornix. No metastases. A patho-anatomical diagnosis was performed but neither the report nor the preparation are retrievable. The only surgical procedure which might, in the opinion of the ophtalmologist, be taken into consideration was enucleation with removal of the eyelid. However, since this was regarded as too extensive an intervention, radium treatment was given by way of experiment in a large dose with a total of 46 mg of radium element for 48 hours at a distance of $1^1/_2$ cm with a leaden filter 3 mm thick. The total dose was calculated to equal 2,208 mg-hours of radium elements.

The treated surface had an extent of approximately $2^1/_2 \times 3$ cm. The treatment was administered through the eyelid. A marked reaction to the irradiation occurred with an epithelial desquamation in an area of 6—8 cm^2. The tumor disappeared quickly. The very next year a beginning atrophy of the eyelid was noticed. The atrophy increased with the years, while the bone parts surrounding the eye were retarded in their

development. The eye was always in a state of irritation, shunning the light. In addition, a cataract was found. Accordingly, 7 years after the treatment, enucleation of the eye was performed and the patient has since been free from symptoms from the tumor.

Two cases of radiation injury after roentgen treatment occurred. One of them concerned a man of 70 years of age, where a strong clinical suspicion of malignancy was entertained from the start owing to a lymph node suggestive of metastasis which was palpated in the neck. The tumor was extirpated first (P-A-D: malignant melanoma) and then roentgen treatment was administered. In a first series about 1,000 r were given, and in a second series about 3 months later approximately 800 r. The tumor did not recur and the lymph node suggestive of metastasis diminished spontaneously. The patient had the same power of vision on both eyes before the treatment, *i.e.* $\frac{L}{R} > 0.7$ with corr. Three years after the treatment, vision began to deteriorate on the treated eye and the ophthalmologist found a posterior corticalis cataract. The other eye still had a clear lens and unchanged power of vision. Three years later, a cataract developed even in the other eye, which was probably senile. The patient was then 76 years of age. He was still living in 1944, and had been free from recurrence for 13 years.

The other patient was a boy of 8 years who had a small yellowish, somewhat elevated spot close to the limbus. It was treated in 1921 with roentgen, but since it only decreased slowly and on one occasion even seemed to increase, very large doses were administered. A total of over 4,000 r were given in about 2 years. In addition, superficial application of 9.4 mg of radium to the tumor rest during $^1/_2$ hour was made about 3 years after the roentgen treatment.

The tumor disappeared almost completely after this treatment and only a slight pigmentation remained. Seven years after the roentgen treatment, a hypertrophic conjunctivitis on the conjunctiva palp. sup. was treated with 1 C-plane of $^1/_2 \times 1$ for 1 hour. Fourteen years after the first treatment a biopsy examination was performed on a small tumor rest in the form of a slight discolourment in an area the size of a grain of rice. P-A-D: benign naevus with radiation changes. In the same year, a cataract was found, chiefly in the posterior pole of the treated eye. In 1942, the power of vision of this eye was 0.6.

The case of radiation injury through the teleradium treatment concerned a patient of 75 years of age with a malignant melanoma (according to the patho-anatomical diagnosis). The tumor was first treated with 1 C-plane of 1×1 for $2^1/_2$ hours. Then, implantation was performed with 1 needle containing 5 mg of radium element for 4 hours, owing to a tumor growth in the periphery of the treatment region and, finally, teleradium was given since the tumor still appeared radioresistant. On a frontal field

and a lateral field approx. 4,800 r were given to the orbit. About 2 months later, enucleation had to be resorted to owing to a glaucoma (P-A-D malignant melanoma?). Two months later, new teleradium was given — a series of approx. 2,000 r per field — and, after another two months, a third series of approx. 4,800 r per field. After these treatments, a few small epithelial defects and sequestra appeared. The wound gradually healed and, about two years after the treatment, the healing was complete and remained thus until the death of the patient from cerebral haemorrhage about 11 years after the first treatment.

As may be derived from the above discussion, the present routine treatment, superficial application of radium, involves but a slight risk of radiation injury to the eye. Only in one out of 46 cases where this particular method was used did a change remain which may be attributed to the radiation. However, in this case the tumor had extended over to the cornea before the treatment. It is therefore not at all unlikely that the tumor left a connective tissue scar after healing which is now manifested as a clouding of the cornea.

SUMMARY

During the years 1920—1940, 66 cases of epibulbar tumours have been treated by radiotherapy at the Radiumhemmet (Radium Institute) in Stockholm. The method of treatment has usually been a surface application of a weakly filtrated radium preparation. The more advanced malign tumours, however, have been subjected to roentgen treatment in large doses. The material comprises 14 cases of malign melanoma. 7 of these cases have been free from symptoms for more than 5 years and most of them have been treated by a combination of radiotherapy and operative action. Further, 7 cases of nevogenous tumours with suspected malignity are included. Of these, 6 have been free from symptoms for over five years usually after a combination of radiotherapy and operative treatment. Of 6 cases of cancer, 4 have been free from symptoms for more than 5 years and 3 of them were subjected to operative and radiation treatment whilst the remaining case was submitted to radiation treatment only. In the other cases, where the most important group consisted of benign nevogenous tumours good results were usually obtained from roentgen treatment only.

The risks of injury to the eye from the rays proved to be very small when using a surface application of a weakly filtrated radium preparation. Only one case of the 46 treated according to this method showed a change which might have been due to injury by the rays. On the other hand, roentgen and teleradium treatment carried far greater risks of radiation injury in the eye.

ZUSAMMENFASSUNG

In den Jahren 1920—1940 wurden im Radiumkrankenhause in Stockholm 66 Fälle von epibulbärem Tumor mit Radiotherapie behandelt. Die Normalmethode zur Bestrahlung des epibulbären Tumors bestand in Oberflächenapplikation von Radiumpräparaten mit geringer Filtration. Klinisch maligne Tumoren wurden in der Regel mit grossen Dosen von Röntgenstrahlen behandelt. Unter den Fällen waren 14 Fälle von malignem Melanom. 7 derselben sind mehr als 5 Jahre lang symptomfrei geblieben, und zwar ist die Mehrzahl dieser Fälle operiert und bestrahlt worden. Das Material umfasst ferner 7 Fälle von nävogenem Tumor mit Verdacht auf Malignität. 6 dieser Fälle sind über 5 Jahre lang symptomfrei geblieben, auch hier in der Regel nach sowohl Bestrahlung als

ach Operation. Von 6 Krebsfällen sind 4 mehr als 5 Jahre lang symptomfrei geblieben. Drei dieser Fälle waren sowohl bestrahlt als auch operiert worden, und nur einer hatte nur Bestrahlungsbehandlung bekommen. Unter den übrigen Fällen, unter denen die gutartigen nävogenen Tumoren die wichtigste Gruppe bilden, wurden in der Regel mit Radiotherapie allein gute Behandlungsresultate erzielt.

Die Gefahr einer Strahlenschädigung des Auges erwies sich als gering, wenn Oberflächenapplikation von Radiumpräparaten mit geringer Filtration zur Verwendung kam. Nur einer von 46 mit dieser Methode behandelten Fällen wies eine Veränderung auf, die vielleicht durch Strahlenschädigung bedingt gewesen sein kann. Andrerseits brachten Röntgen- und Teleradiumbehandlung bedeutend grössere Gefahren einer Strahlenschädigung des Auges mit sich.

RÉSUMÉ

De 1920 à 1940 66 cas de tumeurs épibulbaires ont été irradiées au Radiumhemmet de Stockholm. La méthode normale de traitement fut l'application en surface de radium faiblement filtré. Les tumeurs malignes plus étendues ont cependant reçu de grosses doses de Rayons X. Le matériel comprend 14 cas de mélanomes malins, parmi lesquels 7 n'ont plus présenté, par la suite, aucun symptôme pendant plus de 5 ans; la plupart d'entre eux ont été traités par la radio-thérapie et la chirurgie combinées. Il faut y ajouter 7 tumeurs naeviques où l'on soupçonnait une tendance à la malignité. 6 parmi elles n'ont donné lieu à aucun symptôme pendant plus de 5 années, ici encore, dans la règle, après une combinaison de la chirurgie avec l'irradiation. Sur 6 cas de cancers 4 ont été asymptomatiques pendant plus de 5 ans, 3 d'entre ceux-ci ayant été traités à la fois par les rayons et par la chirurgie, tandis que le dernier fut uniquement irradié. Dans les cas restants, dont le groupe le plus important était constitué par des tumeurs naeviques bénignes, un bon résultat en règle générale fut obtenu par l'irradiation seule.

Les risques de lésions oculaires causées par les rayons étaient légers avec l'application en surface de radium faiblement filtré. Dans un seul cas sur 46 traités par cette méthode on vit apparaître des altérations peut-être attribuables à l'irradiation. En revanche les Rayons Roentgen et le Téléradium comportent un danger nettement plus grand de léser l'œil par la radio-thérapie.

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AUS DER RÖNTGENABTEILUNG DES KREISKRANKENHAUSES IN HALMSTAD, SCHWEDEN (CHEF: DR B. LILJA) UND AUS DER RÖNTGENDIAGNOSTISCHEN ABTEILUNG DER UNIVERSITÄTSKLINIKEN IN LUND, SCHWEDEN (CHEF: DR H. HELLMER)

PHOTOGRAPHISCHE SCHIRMBILDFRAGEN[1]

Vorläufige Mitteilung

von

Martin Lindgren

Während der letzten Jahre wurde auf der Röntgenabteilung in Halmstad in gewissem Umfang eine Schirmbildapparatur für das grosse Bildformat (80 × 80 mm) zur Lungenuntersuchung benutzt. Äussere Umstände wie die dauernd zunehmende Anzahl von Einzel- und Gruppenuntersuchungen, teilweise bedingt durch die militären Einberufungen und den Flüchtlingsstrom, sowie der zunehmende Filmmangel waren der Anlass. Die Anwendung des Schirmbildes machte es wünschenswert, sich ein vorläufiges Urteil über die Qualität des Schirmbildes im Verhältnis zum Röntgenbilde zu schaffen. Eine Überprüfung des Filmmateriales aus photographischem Gesichtspunkt sowie eine kurze Schilderung der angewandten Methodik sowie der damit gewonnenen Ergebnisse wird im folgenden mitgeteilt. In Fragen der wissenschaftlichen Photographie hat Dr. H. Gordon mir wertvolle Hilfe geleistet.

In photographischer Hinsicht sind folgende Faktoren von grösster Bedeutung für die Qualität des Schirmbildes: 1) Das Auflösungsvermögen der photographischen Emulsion, 2) das Auflösungsvermögen des Leuchtschirmes, 3) das Auflösungsvermögen der Optik. Bei einer gegebenen Schirmbildapparatur sind die Punkte 2 und 3 als Konstant zu bezeichnen, während Punkt 1 weitgehenden Variationen unterworfen werden kann.

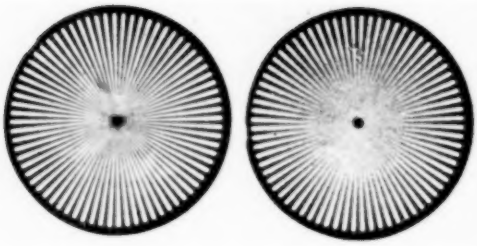
Das Auflösungsvermögen der photographischen Emulsion ergibt sich aus dem Charakter der Emulsion selbst, der durch den Körnigkeitsgrad, die Lichtempfindlichkeit und die Farbempfindlichkeit definiert ist, sowie aus der angewandten Entwicklungstechnik. Hinsichtlich der Körnigkeit liegen die Verhältnisse generell betrachtet stets so, dass die Lichtemp-

[1] Nach einem Vortrag in der Schwedischen Gesellschaft für medizinische Radiologie November 1945; bei der Red. am 4. II. 1946 eingegangen.

findlichkeit mit abnehmender Korngrösse geringer wird. Bezüglich der Farbempfindlichkeit unterscheidet man heute bekanntlich gewöhnliche, auch als farbenblind bezeichnete Emulsionen neben orthochromatischen und panchromatischen. Die gewöhnliche Emulsion ist innerhalb des sichtbaren Spektrums nur für blaue und violette Strahlung empfindlich, im kurzwelligen unsichtbaren Teil dagegen für das gesamte Ultraviolett, so weit dieses nicht durch die Emulsionsgelatine und die Glasoptik selbst absorbiert wird, und schliesslich für alle weiteren Strahlen noch kürzerer Wellenlänge, also auch für Röntgen- und Gammastrahlen. Emulsionen dieses Typus verwendet man in der Röntgenphotographie. In der Schirmbildphotographie hingegen gebraucht man die beiden anderen Emulsionstypen — die orthochromatischen oder panchromatischen — die durch eine Verbreiterung der spektralen Empfindlichkeit bis zum Gelb bezw. Rot charakterisiert sind. Hiermit kann eine Gesamtvergrösserung der Lichtempfindlichkeit überhaupt parallel gehen. Die erwähnte Grundempfindlichkeit der photographischen Emulsion bleibt bei diesen Sensibilisierungsmethoden stets erhalten.

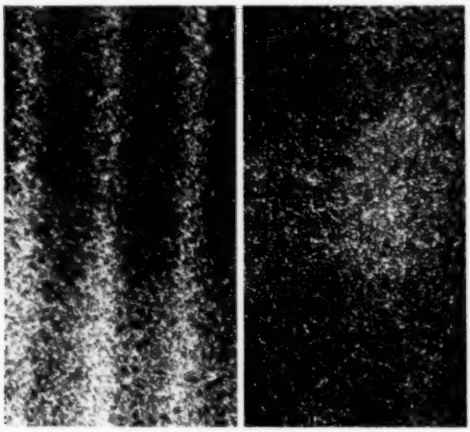
Zur Beantwortung der Frage, ob das grosse Schirmbild an Stelle des Röntgenbildes angewendet werden kann, sind eine Reihe von Untersuchungen ausgeführt worden, die im folgenden teilweise wiedergegeben werden. Der erste Schritt war, einige Röntgenbilder (30 × 30 cm) mit bestmöglicher Technik auf das Schirmbildformat zu verkleinern und andererseit einige Schirmbildaufnahmen von den gleichen Patienten auf das Röntgenbildformat zu vergrössern. Es ist durchaus klar, dass der Wert einer derartigen Untersuchung begrenzt ist; sie dürfte jedoch ein gewisses Interesse haben. Die Resultate bekräftigten früher gemachte Erfahrungen, dass der Detailreichtum in den verkleinerten Röntgenbildern grösser zu sein scheint als in den Originalschirmbildern und in den vergrösserten Schirmbildern kleiner als in den Originalröntgenbildern. Diese Variationen im Detailreichtum scheinen durch Unschärfe im Schirmbilde bedingt zu sein. Einen objektiven Eindruck von dieser Unschärfe erhält man durch die Photographie des Jewell-Franke'schen Sternes (Fig. 1). Im Röntgenbild findet man keinerlei Unschärfe, dagegen tritt diese im Schirmbild deutlich hervor; die Grösse des unscharfen zentralen Teiles gestattet eine quantitative Analyse. Beim Vergleich zwischen Schirmbild und Röntgenbild in Originalgrösse zeichnet sich das Schirmbild bei technisch vollwertigen Bildern durch einen vorzüglichen Kontrast aus, wodurch pathologische Veränderungen im Lungenparenchym oft deutlicher hervorzutreten scheinen als im Röntgenbild.

Die Bildschärfe ist in nicht unwesentlichem Grade vom Bildkorn abhängig; aus diesem Grunde wurde es einer näheren Betrachtung unterzogen. Mikroaufnahmen (Vergrösserung linear stets 31 mal) der Röntgenbilder zeigten ein ausserordentlich kräftiges Korn; die Schirmbilder zeig-



a. b.

Fig. 1. Schärfeunterschiede, dargestellt durch Photographie des Jewell-Franke'schen Sternes. a) Röntgenbild, b) Schirmbild.



a. b.

Fig. 2. Mikrophotographien (Vergrösserung linear 31 mal) zur Darstellung der Bildkorngrösse. a) Röntgenbild, b) Schirmbild.

ten ein wesentlich kleineres Korn (Fig. 2). Das Bildkorn des Röntgenbildes entsteht aus der Summe zweier verschiedener kornartiger Elemente, nämlich dem Korn der Verstärkungsfolien und dem Korn der lichtempfindlichen Emulsion. Nur das letztere hat hier ziemlich grobe Dimensionen, die auf dem fertigen Bilde durch die doppelseitige Filmschicht sowie durch die übliche Entwicklung in stark alkalischen Entwicklern, die das mögliche Silberkorn zu seiner vollen Entfaltung bringen, noch weiter hervorgehoben werden. Beim Schirmbild entsteht das Bildkorn aus den feinen Körnern der lichtempfindlichen Emulsion und aus der optischen Abbildung der Körner des Leuchtschirmes, die selbstverständlich stark verkleinert wiedergegeben werden.

Aus der Schirmbildliteratur geht hervor, dass die Korngrösse des Leuchtschirmes von wesentlicher Bedeutung für die Detailwiedergabe des Schirmbildes ist. Die Korngrösse des Leuchtschirmes ist bedeutend gröber als die der Verstärkerfolien. Auch unter Berücksichtigung der Verkleinerung durch die Optik ist dieser Umstand für die Bildwiedergabe auf dem Film ungünstig, denn das Bildkorn wird zum grossen Teil durch das grobe Korn des Schirmes geschaffen. Leider verhält es sich zur Zeit so, dass man mit Rücksicht auf die notwendigen Energiemengen gezwungen ist, einen Kompromiss zwischen der photographischen Aktinität und der mittleren Korngrösse des Schirmes zu

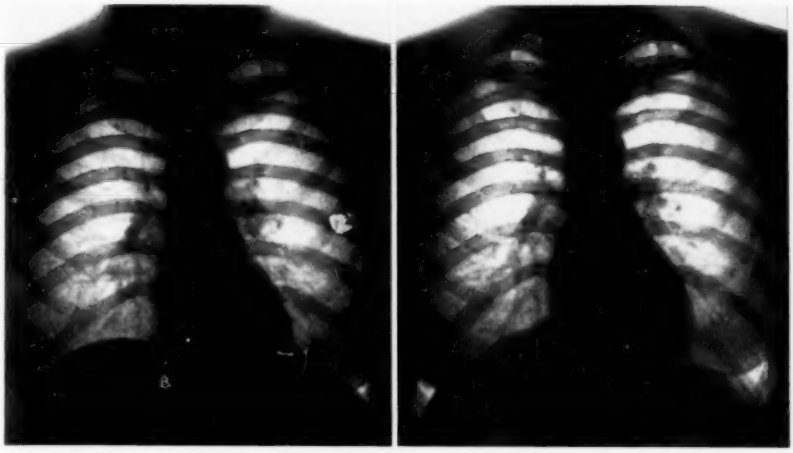


Fig. 3 a. Hasselbladbild. Fig. 3 b. Meritolbild.

schliessen, da eine befriedigende Lösung der einen Bedingung unvorteilhaft auf die andere einwirkt.

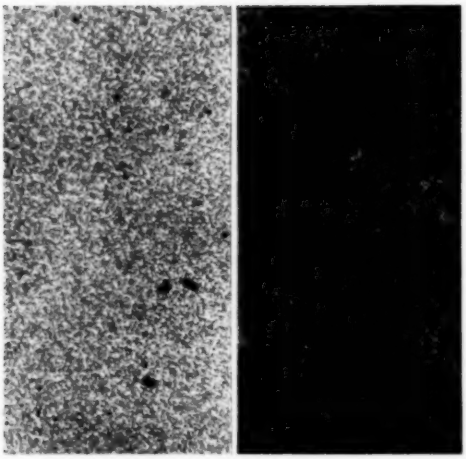
Jedes Leuchtschirmkorn deckt nicht nur ein Korn der Filmemulsion sondern — zum mindesten teilweise — noch mehrere andere. Werden nun die Emulsionskörner von Lichtstrahlen getroffen, geschieht in der Entwicklung deren vollständige Schwä zung und hierdurch macht sich eine Konturunschärfe im Bilddetail geltend.

Diese Betrachtungen veranlassten zu dem Versuch, die Detailwiedergabe des Schirmbildes durch Verkleinerung des Emulsionskornes in der Entwicklungsphase zu verbessern.

Zu diesem Zwecke wurden 9 verschiedene Entwickler geprüft.[1] Die Schirmbilder wurden in üblicher Weise exponiert.

Bei Anwendung von Feinkornentwicklern wird die Verkleinerung der Silberkörner durch Senkung der Alkalität der Entwicklerlösung und durch Zusatz von bromsilberlösenden Substanzen erreicht. Auf Einzelheiten in der Zusammensetzung der verschiedenen Entwickler und deren Wirkungsweise gehe ich nicht ein, sondern referiere nur einige der Resultate, nämlich die mit Hasselblads Röntgenentwickler und mit dem »echten» Feinkornentwickler Meritol erzielten. Meritol Nr. 100 ist ein englischer Entwickler, dem in der Literatur ausgezeichnete Eigenschaften

[1] Hasselblads Spezial Röntgenentwickler, Glycin-Soda Entwickler; Kodak DK 76, Kodak DK 20, Brenzkatechin, Metol; Meritol Nr. 100, Paraamidophenol, Ortho-Phenylendiamin.



a. b.

Fig. 4. Mikrophotographien (Vergrösserung linear 31 mal) zur Darstellung der Bildkorngrösse. a) Hasselbladbild, b) Meritolbild.

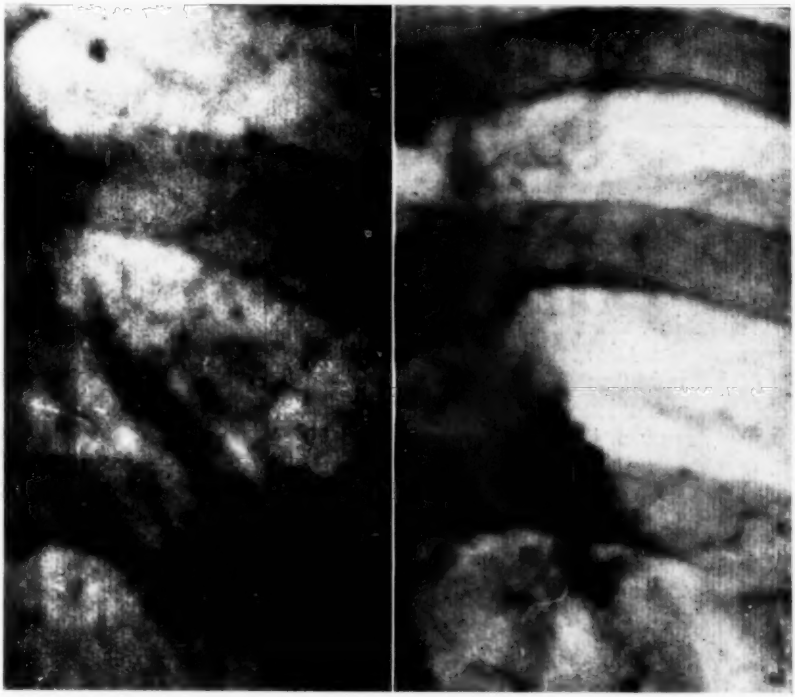
zugeschrieben wurden. Das Meritol, welches hier nicht im Handel zugänglich war, wurde zu diesem Zweck synthetisch hergestellt.

Das Hasselbladbild (Fig. 3 a) ist 5 Minuten lang entwickelt worden, das Meritolbild (Fig. 3 b) 40 Minuten lang. Die Entwickler sind frisch hergestellt worden, so dass keinerlei Ausnutzungsfaktoren ihre Wirkung abschwächen konnten. Rein visuell betrachtet ist die Wiedergabe der Einzelheiten auf dem Hasselbladbilde gut. Im Meritolbilde ist die Detailwiedergabe jedoch sämtlichen hier geprüften Entwicklern völlig überlegen.

Der subjektiv gewonnene Eindruck wird durch Mikrophotographien dieser Schirmbilder bekräftigt (Fig. 4). Beim Vergleich tritt mit grosser Deutlichkeit die Überlegenheit des Feinkornentwicklers hervor. Um den Wert der Feinkornentwicklung augenfällig zu demonstrieren, sind Teilvergrösserungen eines in Halmstad mit Hasselbladentwickler angefertigten Routinebildes und eines Meritolbildes hergestellt worden. Bei einer zweifachen Vergrösserung tritt bereits die bessere Qualität des Meritolbildes hervor; ein wesentlicher Unterschied in der Wiedergabe feinerer Einzelheiten zwischen beiden Entwicklungsmethoden ist jedoch noch nicht wahrnehmbar. Bei sechsfachen Vergrösserung (Fig. 5) kann man im Meritolbild noch deutlich Details wahrnehmen, die das Hasselbladbild nur unscharf wiedergibt.

Für die tägliche Schirmbildarbeit hat diese Entwicklungsmethode auf Grund des Zeitverlustes bisher keinen praktischen Wert gehabt. Kann jedoch die Entwicklungsdauer wesentlich herabgesetzt werden, was mit grösster Wahrscheinlichkeit möglich ist, hat die Methode sowohl für das Schirmbild als auch vielleicht für das Röntgenbild bei gewissen Fragestellungen ihren gegebenen Platz. Schon in ihrer gegenwärtigen Form dürften die sog. »echten» Feinkornentwickler den Versuch gestatten, Schirmbildaufnahmen von Massenuntersuchungen zu entwickeln; die Entwicklungsdauer dürfte in diesem Falle ohne grössere Bedeutung sein.

Der Umstand, dass der Fluorapidfilm laut Angabe für das gelbgrüne



a. b.

Fig. 5. Teilvergrösserungen (× 6) von a) Hasselbladbild, b) Meritolbild.

Licht des Leuchtschirmes sensibilisiert ist, veranlasste eine nähere Untersuchung dieser Faktoren in der Absicht, ihre Einwirkung auf die Bildqualität zu ermitteln. Die Sensibilisierungskurve des Agfa-Fluorapidfilmes wurde, obwohl sie in der Literatur wiedergegeben ist, einer Nachprüfung unterzogen und in vollem Einklang mit den Originalangaben befunden. Ihr Verlauf (Fig. 6) ist folgender: Im Ultraviolett beginnt die übliche Eigenempfindlichkeit des photographischen Negativmateriales in allen mit Glasoptik ausgestatteten Apparaten bei 360 mμ. Sie zeigt einen allmählichen Anstieg, erreicht ein Maximum bei 430 mμ und bleibt dann annähernd konstant, bis sie bei 580 mμ, also im hellen Gelbgrün, ihre grösste Empfindlichkeit zeigt. Danach folgt ein ziemlich steiler Abfall der Kurve, die im Orange noch eine schwache weitere Empfindlichkeit aufweist. Diese Empfindlichkeitskurve ist charakteristisch für ein Negativmaterial mit höchster Orthochromasie und Neigung zu Panchromasie.

Fig. 6.

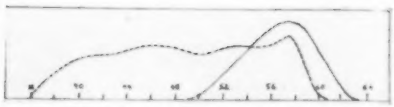


Fig. 7.

Fig. 6. Sensibilisierungskurve des Agfa-Fluorapidfilmes (Hilger-Spektrograph).
Fig. 7. Verlauf der Kurven für die spektrale Empfindlichkeitsverteilung des Fluorapidfilmes (------) und für die Spektralverteilung der Lichtemission im Neossalschirm (———).

Weiterhin wurde eine Prüfung der Lichtemission des Neossalschirmes vorgenommen. Die angewandte Apparatur zeigte eine maximale Spannung von 60 kV bei 20 m A. Bei dieser Belastung konnte in einem Zeiss Handspektroskop ein Emissionsband beobachtet werden, das sich von etwa 490 mμ bis etwa 630 mμ erstreckte, mit dem Maximum bei etwa 580 mμ. Es konnten keinerlei weitere Emissionen in anderen Teilen des Spektrums beobachtet werden. Quantitative Messungen sind in diesem Zusammenhang nicht vorgenommen worden.

Vergleicht man die beiden Kurven für die spektrale Empfindlichkeitsverteilung des Fluorapidfilmes einerseits und für die Spektralverteilung der Lichtemission im Neossalschirm andererseits (Fig. 7) so ergibt sich folgender Sachverhalt. Die Empfindlichkeit des Fluorapidfilmes wird nur in dem Bereich der maximalen Emission des Schirmes vollständig ausgenutzt. Es wird weiterhin ein Teil der Grünempfindlichkeit bis zu 490 mμ zum Aufbau des Bildes verwendet, ferner ein noch sehr viel geringerer Teil nach der orangeroten Seite zu, wo die Filmempfindlichkeit bei etwa 600 mμ aufhört, während die Schirmemission sich noch weiter bis etwa 630 mμ erstreckt. Vollkommen ausser Wirkung gesetzt aber wird der ganze wichtige Empfindlichkeitsteil der Emulsion, der zwischen 490 mμ und 360 mμ bezw. noch weiter im ultravioletten Teil liegt.

Die Anpassung von Filmsensibilisierung und Leuchtschirmemission ist demnach ziemlich gut, kann aber zum mindesten nach der orangeroten Seite noch verbessert werden.

Durch die geschilderte Anpassung entsteht ein Effekt, der eine gewisse Analogie zu einer Aufnahmetechnik darstellt, bei der man beispielsweise in der normalen Photographie irgendein Motiv durch Anwendung eines Gelbgrünfilters mit deutlicherer Wiedergabe der Einzelheiten infolge Kontraststeigerung zur Darstellung bringt. In diesem Falle nimmt das Filter — je nach seiner Intensität — den grössten Teil störender blauer bezw. violetter Strahlung fort, die stets eine Verflachung der Gradation bewirkt. Wenn man, um ein weiteres Beispiel zu nehmen, in der normalen Photographie ein beliebiges Motiv durch jeweils ein

rotes, ein gelbgrünes und ein blaues Filter photographiert, zeigt es sich, dass stets das gelbgrüne Filter die beste Wiedergabe der Einzelheiten aufweist. In der medizinischen Diagnostik macht man sich diese Tatsache bei der Mikrophotographie zunutze. Wenn nicht die Eigenfarbe des wiederzugebenden Objektes spezielle Filter notwendig macht, wird stets ein gelbgrünes bis grünes Filter mit bestem Erfolge zur Verbesserung der Wiedergabe der Einzelheiten benutzt.

Bei der Schirmbildphotographie strahlt der Leuchtschirm nur gelbgrünes Licht aus, dessen Spektralbereich, wie wir sahen, sich von Grün bis Rot erstreckt. Der blaue bezw. der violette Teil der Emulsion wird somit zum Bildaufbau nicht benutzt und eine Verflachung der Gradation dadurch vermieden. Auf diese Weise kommt es zu einer Kontraststeigerung. Die Farbensensibilisierung des Filmes gewährleistet eine Empfindlichkeit gerade für dieses »gefilterte» Licht; hierdurch kommt eine weitere Steigerung des Kontrastes zustande (im Gegensatz zum unsensibilisierten Film). Die so erzielte Verbesserung der Detailwiedergabe ist von grosser Bedeutung.

Zusammenfassend kann man sagen, dass der Detailreichtum im Schirmbild geringer zu sein scheint als im Röntgenbild. Dieses ist bedingt durch Schärfeverlust im Schirmbildsystem.

Verbesserungsmöglichkeiten wurden aufgezeigt, teils durch Feinkornnentwicklung, teils durch bessere Anpassung der Licht- und Farbempfindlichkeit zur spektralen Emission des Leuchtschirmes.

Der auffallende Kontrastreichtum des Schirmbildes, der, wie man im allgemeinen sagt, auf Abwesenheit detaillierter Zeichnung und Unschärfe beruhen soll, *dürfte zum mindesten teilweise durch die beschriebene Filterwirkung und die Filmsensibilisierung seine Erklärung finden. Es muss hierzu noch einmal hervorgehoben werden, dass der gute Kontrast den Eindruck gesteigerter Schärfe hervorruft.*

Nun einige Worte über unsere Methode, das Schirmbild in der täglichen Routinearbeit im Krankenhaus anzuwenden. Unsere Methode ist eine Modifikation der vollständigen Röntgenuntersuchung, bei der das Röntgenübersichtsbild durch das Schirmbild ersetzt und Durchleuchtung in allen unklaren Fällen ausgeführt wird.

Die Prüfung des grossen Schirmbildes für Lungenuntersuchungen im Rahmen der täglichen Arbeit auf der röntgendiagnostischen Abteilung erstreckt sich bereits über einen Zeitraum von $2^1/_2$ Jahren.

Das Schirmbildsystem besteht aus dem Standardstativ von Schönander und einer Siemens P-40 Röhre, die an einen 6-Ventilapparat vom Typus Tridoros gekoppelt sind. Filmmaterial: Agfa-Fluorapid 80 × 80 mm. Entwickler: Hasselblad.

Die Röntgenbilder, mit welchen die Resultate verglichen wurden,

sind mit dem gleichen 6-Ventilapparat und P-40 Röhre auf übliche Art und Weise hergestellt worden.

Vor Einfügung der Methode in den Arbeitsgang war ein Überblick über ihre Effektivität notwendig. Aus diesem Grunde wurden während der ersten Zeit von allen mit Schirmbild untersuchten Patienten — etwa 200 — auch Röntgenbilder der Lungen hergestellt. Während dieses Zeitraumes haben wir keinen Fall finden können, wo das Schirmbild auf dem Röntgenbilde sichtbare Veränderungen nicht zur Darstellung brachte. Dieses Ergebnis ermunterte dazu, das Röntgenübersichtsbild durch das Schirmbild zu ersetzen. Folgender Untersuchungsgang stellte sich als zweckmässig heraus: Jeder Lungenpatient, der stehen kann, wird schirmbilduntersucht mittels Frontal- och Seitenaufnahme. Nachdem man sich mit Hilfe des Verweisungsscheines mit dem Fall vertraut gemacht hat, wird der nasse Film sofort beurteilt. Die Prüfung geschieht mit Hilfe eines Binokels mit mässiger Vergrösserung. Technisch vollwertige Bilder sind genau so wie bei der Röntgenphotographie eine unabweisbare Forderung. Wird auf dem Schirmbilde etwas entdeckt, was nicht ganz klar ist, wird sofort die Durchleuchtung angeschlossen und ev. notwendige Spezialaufnahmen werden hergestellt.

Unser Material vom $^{15}/_{3}$ 1943 bis $^{15}/_{9}$ 1945 umfasst 5,606 Lungenuntersuchungen. In 1,646 Fällen ist ausschliesslich die Röntgenuntersuchung ausgeführt worden. In 3,960 Fällen wurde das Schirmbild benutzt; dieses wurde in 970 Fällen (25 %) durch gezielte Röntgenaufnahmen komplettiert. Durch derartige Vergleiche zwischen Schirmbild und Röntgenbild in nahezu 1,000 Fällen haben wir umfangreiche Erfahrungen bezüglich des Wertes einer technisch guten Schirmbildaufnahme gewonnen.

Während des Zeitraumes von $2^{1}/_{2}$ Jahren haben wir den geschilderten Untersuchungsgang angewendet und keinen Beweis für einen Schirmbildsversager erhalten.

Eine endgültige Beantwortung der Fragestellung: »Kann das Schirmbild bei Lungenuntersuchungen das Röntgenübersichtsbild ersetzen?» kann noch nicht geschehen. Die gewonnenen praktischen Resultate dürften uns — unter gleichzeitiger weiterer Penetration der physikalischen Fragen — jedoch dazu berechtigen, in der angedeuteten Weise fortzusetzen.

ZUSAMMENFASSUNG

Die in gewissem Umfang erfolgende Anwendung einer Schirmbildapparatur (Filmformat 80 × 80 mm) für Lungenuntersuchungen veranlasste eine aus photographischem Gesichtspunkt durchgeführte Prüfung der Qualität des Schirmbildes im Verhältnis zum Röntgenbilde.

Es ergab sich, dass der Detailreichtum im Schirmbild geringer zu sein scheint als

im Röntgenbild. Die Ursache ist bedingt durch Schärfeverlust im Schirmbildsystem. Verbesserungsmöglichkeiten wurden aufgezeigt, teils durch Anwendung eines Feinkornentwicklers, teils durch bessere Anpassung der Licht- und Farbempfindlichkeit zur spektralen Emission des Leuchtschirmes. Der auffallende Kontrastreichtum des Schirmbildes, der, wie man im allgemeinen sagt, auf Abwesenheit detaillierterZeichnung und Unschärfe beruhen soll, dürfte zum mindesten teilweise durch die beschriebene Filterwirkung seine Erklärung finden. Es muss hierzu noch einmal hervorgehoben werden, dass der gute Kontrast den Eindruck gesteigerter Schärfe hervorruft. In der Zeit vom 15. 3. 1943 bis 15. 9. 1945 sind 3,960 Schirmbilduntersuchungen von Lungen ausgeführt worden; diese wurden in 970 Fällen (25 %) durch gezielte Röntgenaufnahmen komplettiert. Während dieses Zeitraumes hat man keinen Beweis für einen Schirmbildversager erhalten.

SUMMARY

The use of a photofluorographic apparatus (size of film: 80 × 80 mm) for examining the lungs led to test, from the photographic point of view, the quality of the photofluorographic picture in relation to the roentgen picture.

It appeared from this that the richness in detail of the photofluorographic picture seems to be less than that of the roentgen picture. The reason is a loss of sharpness within the photofluorographic system. The author points out some possibilities for improvement, viz. the use of a fine-grain developer and a more suitable adaption of the actinic and colour sensitivity of the emulsion to the spectral emission of the screen. The obvious richness of contrast in the photofluorographic picture, which is usually considered to depend on the lack of details and sharpness, is at least partly explained by the action of the filter described by the author. In this respect it is pointed out that the good contrasts also give the impression of increased sharpness. From $^{15}/_{3}$ 1943 to $^{15}/_{9}$ 1945, 3,960 photofluorographic examinations of the lungs have been carried out. In 970 cases (25 %) these were complemented by detailed radiographs. During these two and a half years no evidence of an unsuccessful photofluorographic picture has appeared.

RÉSUMÉ

L'emploi assez étendu d'un appareil de radiophotographie (format des films: 80×80 mm) pour des examens pulmonaires a amené à préciser du point de vue photographique la qualité de l'image radiophotographique comparée à celle de la radiographie.

On a constaté que la richesse en détails semble être moindre sur la radiophotographie que sur la radiographie. La cause en est une perte de netteté dans le système radiophotographique. L'auteur montre des possibilités d'amélioration, d'une part en se servant d'un révélateur pour émulsion à grain fin, d'autre part en adaptant à l'émission spectrale de l'écran fluorescent la sensibilité du film à la lumière et à la couleur. La richesse frappante en contrastes de la radiophotographie qui, à ce qu'on dit communément, tiendrait à l'absence de détails dans le dessin et au flou, devrait pour le moins être expliquée en partie par l'effet de filtre que l'auteur a décrit. A ce sujet il faut encore une fois souligner que les bons contrastes créent l'impression d'une augmentation de la netteté. Du 15. 3. 43 au 15. 9. 45 il a été fait 3,960 examens radiophotographiques; ceux-ci furent complétés dans 970 cas (25 %) par des radiographies. Pendant ce laps de temps on n'a eu aucune preuve d'un échec imputable à la radiophotographie.

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AUS DER RÖNTGENDIAGNOSTISCHEN ABTEILUNG DES KAROLINISCHEN KRANKENHAUSES, STOCKHOLM (VORSTAND: PROF. Å. ÅKERLUND)

GÜRTEL FÜR KOMPRESSION DER URETEREN[1]

von

Erik Lundström

Die gewöhnliche Weise, um Stauung in den Ureteren hervorzurufen, ist ein breites Tuchband mit Spannmechanismen an den Kanten des Untersuchungstisches quer über den unteren Teil des Bauches des Patienten zu spannen. Unter diesem Band werden ein oder zwei verhältnismässig fest gestopfte Kissen angebracht, die durch den Druck des Bandes gegen die Ureteren gepresst werden. Dieses Kompressionsverfahren ist häufig sehr unbequem für die Patienten, sowohl zufolge des unelastischen Druckes als auch dadurch dass der Patient gegen den harten Untersuchungstisch gepresst wird, was besonders für magere Patienten sehr schmerzhaft sein kann. Auch röntgenologisch ist diese Methode nicht so günstig, weil die Fixierung des Patienten an dem Tisch wesentlich die Möglichkeiten die Projektionen zu variieren begrenzt, da diese Fixierung Schräglage des Patienten verhindert.

Gürtelartige Kompressionsanordnungen, wo der Patient frei am Tische liegt und wo die Kompression durch das Aufpumpen einer Gummiblase zwischen dem Gürtel und dem Bauch ermöglicht wird, werden deshalb mehr und mehr verwendet. Die Kompression mit Gummiblase ist weit schonsamer auf Grund eines mehr elastischen und gleichmässig verteilten Druckes.

Im Jahre 1937 veröffentlichte der Verfasser eine solche Gürtelkonstruktion[2] welche im Laufe der Jahre gewisse Abänderungen erfahren hat. Das letzte Modell[3] besteht aus folgenden Teilen (siehe Fig. I):

1) Dorsaler Teil aus Tuch mit Band und Schnallen. (A)

2) Ventraler Schild (B) aus durchsichtigem Material mit geringer Absorption gegenüber Röntgenstrahlen mit vier Schlitzen für die Bänder versehen.

[1] Bei der Red. am 12. IV. 1945 eingegangen.

[2] »Nordisk Medicinsk Tidskrift 1937», Bd. 14, Seite 1722.

[3] Hersteller: Järnhs Elektriska A/B, Stockholm.

3) Kompressionsblase aus Gummi (C) 3 Grössen Nr 1, 2 und 3 (gewöhnliche Fussballblasen).

4) Manometer (D) in mm Hg gradiert und 2 Ventile (E und F) auf einer Bakelitplatte montiert.

5) Gummipumpe (G).

Vor der Kompression wird der Patient in Rücklage auf den Untersuchungstisch mit Kissen unter dem Kopf und den Knien gelegt.

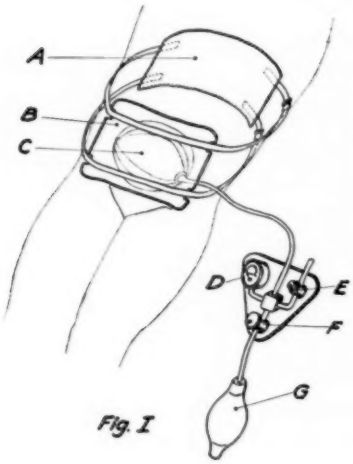


Fig. I

Bei der Anlegung des Gürtels für Kompression der *beiden* Ureteren wird erst der dorsale Teil unter die Sacralregion des Patienten angebracht und mit den Bändern um den Bauch festgespannt so, dass das untere Band etwas höher als die Symphyse liegt. Danach wird die leere Kompressionsblase (für Erwachsene meistens Grösse Nr 3) quer über den unteren Teil des Bauches gelegt, etwa 3 Querfinger von der Symphyse. Auf die Gummiblase wird der Schild quer angebracht. Die Bänder werden über die Kanten des Schildes in die Schlitze geschoben, und die Blase wird *langsam* bis zu einem Druck von etwa 40—80 mm Hg aufgepumpt. Der anzuwendende Druck ist von Tonus in den Bauchmuskeln und die Fähigkeit des Patienten, den Druck auszuhalten, abhängig. Der untere Teil der Blase darf nicht gegen die Symphyse anliegen sondern soll ein Paar Querfinger höher als dieselbe liegen. Korrigierungen der Lage der Blase sind oft notwendig. Will man den Kompressionsdruck verringern, wird ein Teil der Luft in der Blase durch Druck auf das Ventil E herausgelassen. Zum Schluss wird zweckmässig das Ventil F zu der Gummipumpe durch Linksdrehung der Kordonschraube zugeschraubt, weil das in der Gummipumpe eingebaute Ventil im Allgemeinen nicht genügend dicht ist.

Während der Kompression soll der Patient nicht die Bauchmuskulatur spannen, weil dadurch die Ureterenkompression verringert oder aufgehoben wird. Besonders aktives Heben von Kopf und Beine soll vermieden werden. Die für die verschiedenen Projektionen notwendigen Lageveränderungen werden ohne aktive Mitwirkung des Patienten durchgeführt. Durch Kissen o. dgl. soll man danach streben, dass der Patient so bequem wie möglich liegt um Bauchmuskelkontraktionen zu vermeiden. Ab und zu soll man den Druck des Manometers kontrollieren.

Es ist empfehlenswert, den Patienten darauf aufmerksam zu machen, sofort anzumelden, wenn der Druck infolge Undichtheit sich verringern sollte. Falls Undichtheit in den Gummischläuchern entsteht, kann man durch einen Peang die Anschlussleitung der Kompressionsblase zusammenklemmen.

Bei Kompression von nur der *einem* der Ureteren wird in derselben Weise wie oben mit dem Unterschied verfahren, dass eine kleinere Blase (Nr 1 oder 2) verwendet wird, die über den betreffenden Ureter angebracht wird.

Bei Beendigung der Kompression drückt man mit der einen Handfläche gegen den Schild und schiebt mit der anderen Hand die Bänder aus den Schlitzen über die Kanten des Schildes. Der Schild und die Blase können jetzt entfernt werden, während der dorsale Teil des Gürtels unter der fortgesetzten Untersuchung liegen bleiben kann.

Ureterenkompression, die bei intravenöser Urographie sich als ein sehr gutes diagnostisches Hilfsmittel gezeigt hat, kann auch bei retrograder Pyelographie verwendet werden. In diesem Falle werden *erst*, am Besten während der Durchleuchtungskontrolle, die Nierenbecken mit Kontrastmittel gefüllt und *danach* die Ureteren mit den zurückgebliebenen Kathetern komprimiert. Unter anderem sind dabei stereoskopische Radiogramme über die oberen Teile der Urinwege leicht zu erhalten, was ab und zu die Beurteilung der Formveränderungen erleichtert.

ZUSAMMENFASSUNG

Verfasser beschreibt eine gürtelartige Anordnung für Kompression der Ureteren bei sowohl intravenöser Urographie als retrograder Pyelographie. Eine schonsame Kompression wird erreicht. Die Fixierung des Patienten an dem Untersuchungstisch wird vermieden.

SUMMARY

The author gives a description of a girdle-shaped contrivance for compression of the ureters at intravenous urography as well as at retrograde pyelography. By this means a gentle compression is obtained. Fixation of the patient to the examination table is avoided.

RÉSUMÉ

L'auteur décrit un dispositif de compression en forme de ceinture pour la compression des uretères dans l'urographie intraveineuse et la pyélographie rétrograde. Il permet une compression douce et rend inutile la fixation du malade à la table d'examen.

FROM THE ROENTGEN DIAGNOSTIC DEPARTMENT, KAROLINSKA SJUKHUSET, STOCKHOLM
(CHIEF: PROFESSOR ÅKE ÅKERLUND)

TWO MECHANICAL DEVICES FOR REDUCING THE RISK OF RADIATION EXPOSURE DURING CERTAIN TYPES OF ROENTGEN EXAMINATIONS[1]

by

B. J. Markman

1. Distant manipulation of the contrast medium syringe in urethrographic examinations in the male.

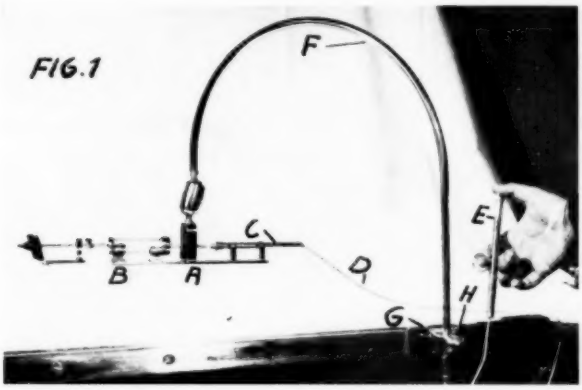
In urethrography with retrograde injection of contrast medium the exposure must be made while the injection is in progress if the prostatic portion of the urethra is to be visualized on the roentgenogram.

When Knutsson's apparatus is used the examiner comes in close proximity to the examination field and is exposed to a great deal of scattered radiation. Investigations carried out at the Institute of Radiophysics of King Gustav V's Jubilee Clinic have proved that ungloved hands manipulating the contrast medium syringe and protected by nothing but a pair of lead-impregnated gloves placed *over* the hands, as is the custom usually adopted, are exposed to a dose of about 0.18—0.30 r per patient (an average of 85 K. V., 250 Ma, 0.6 sec. per exposure and 3—5 exposures per patient). Under similar conditions unguarded parts of the trunk are exposed to 0.003—0.005 r per patient. If the number of the urethrographic examinations are as many as 5 to 6 a day as is the case at the Roentgen Department of Karolinska Sjukhuset, the hands receive a daily dose of about 1—1.5 r, which is 4 to 6 times the daily tolerance dose according to Mutscheller.

With a view to eliminating this radiation an apparatus has been constructed that makes it possible to manipulate the syringe from a distance of 1.5—2 m. The examiner can at the same time stand protected behind a door or a screen covered with lead.

Other authors have devised contrivances for the same purpose,

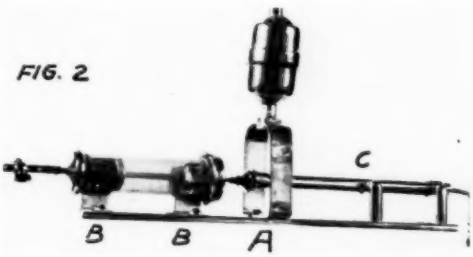
[1] Submitted for publication, Jan. 2, 1946.



MARCEL, who uses an apparatus resembling that of KNUTSSON, elongated the cannula of the syringe so that the hands would be separated by a distance of about 35 cm from the exposed area.

The appearance of the apparatus described in the present paper is clearly illustrated in Figs. 1 and 2.

On a metal plate A are placed two holders B for the syringe, and a movable piston C attached to two supports of metal. From this piston there extends a flexible metal tubing, D, about 1.5 m long with a pianowire running through it. The other end of this is fastened to a plunger E, which is shaped like the handle of an ordinary wound syringe. The metal tubing and piano-wire are adjusted in such a way, that pressure on the plunger E causes the tubing to move forward, this movement being carried through to the piston which in its turn presses the plunger of the syringe forward. Because of the smooth surface of the piano-wire and the presence of oil between the wire and the tubing the friction is inconsiderable and does not to any great extent prevent the operator from feeling whether there is any resistance to the injection.



The metal plate is movable attached by means of a holder and a ball and socket joint to an arched metal rod F, which can be fastened by an adjusting screw H to the movable bracket G on the edge of the examination table.

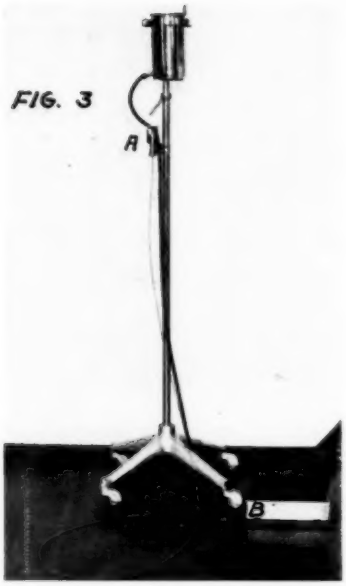


FIG. 3

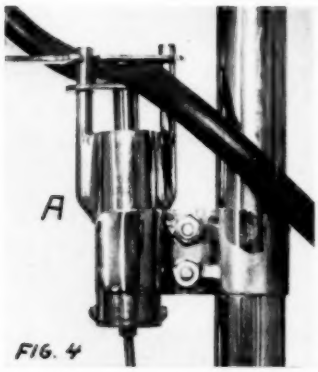


FIG. 4

This arrangement allows the syringe to be readily adjusted to every position required for the examination.

The fact that the syringe is fastened in the holders has the added advantage that the injection instrument can be kept motionless during exposure, a circumstance which is not always so when the syringe is held in the hand.

This apparatus has been in daily use for more than six months in our Department, and has been found to function satisfactorily.

2. Regulation by the foot of the administration of barium enema in examinations of the colon.

In examinations of the colon the administration of the barium enema is usually regulated by means of a strong spring clip on the rubber tubing running from the can resevoir.

The spring clip is manipulated either by an assistant or by the examiner's right hand, which must then be ungloved.

The assistant or the right hand of the examiner is in the meantime exposed to scattered radiation. In order to eliminate this, we have devised a regulating contrivance capable of being worked by the foot and allowing the examiner to work with lead-impregnated gloves on both hands.

The construction of the apparatus will be clear from Figs. 3 and 4.

On the rubber tubing there is a gripping appliance at which the pressure on the tubing is exerted by a strong coiled spring situated in the container A. This spring can be compressed through a wire in a flexible metal tubing by pressure on a pedal B.

This apparatus has been in constant use for some months and has proved satisfactory.

The apparatuses have been constructed by the Department of Precision Mechanics, Karolinska Sjukhuset, and can be obtained from Järnhs Elektriska A. B. Stockholm.

SUMMARY

This paper describes a new apparatus for distant manipulation of the contrast medium syringe in urethrographic examinations and the administration of the enema in examinations of the colon, intended to reduce the radiation risk for examiner or assistants.

ZUSAMMENFASSUNG

Beschreibung einer neuen Apparatur zur Maneuvrierung aus der Entfernung der Kontrastspritze bei Urethrozystographie und der Kontrastzufuhr bei Kolonuntersuchung, in beiden Fällen zur Herabsetzung der Strahlungsgefahr für den Untersucher oder assistierendes Personal.

RÉSUMÉ

Description d'un nouvel appareillage pour manœuvrer à distance le seringue avec son liquide opacifiant dans l'urétro-cystographie et introduire à distance aussi le lavement de contraste dans le côlon, de façon à diminuer dans les deux cas le risque de de la radiation pour le médecin et le personnel qui l'assiste.

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INTRAVASCULAR AND EXTRAVASCULAR PRESSURE IN VALSALVA'S EXPERIMENT[1]

by

Gunnar Moberg

There has recently appeared in the literature a statement to the effect that the blood pressure in the pulmonary artery can be determined by measuring the intrabronchial pressure arising during Valsalva's experiment. The method is based on the fact that the volume of the pulmonary artery decreases during the course of Valsalva's experiment, as well as on the assumption that this decrease occurs when the intrabronchial pressure has reached the same level as the pressure in the pulmonary artery.

Even in the early days of the radiologic era it was observed that the amount of blood in the heart and intrathoracic vessels shows considerable variation with varying physiologic conditions. The view held by earlier observers, that the normal heart becomes dilated in connection with severe exertion, was exploded in 1904 by DE LA CAMP, who found that there was no dilatation of the heart under these conditions and that occasionally there could even occur a decrease in volume. In 1907, KIENBÖCK, SELIG and BECK showed that as a rule a normal heart more or less decreases in size after strong exertion, when the exertion has been carried to such a degree that complete bodily exhaustion of the subject under observation has resulted. Another observation is that made by MORITZ in 1904, who found that the normal heart is generally smaller when the subject stands erect than when he is lying in the horizontal position. At an early stage also, it was observed that small changes in cardiac volume occur in normal respiration. With regard to this finding, the results obtained by different investigators were to a certain extent contradictory, but this is very likely to be explained by the fact that we are dealing here with fairly small changes in volume. The commonest occurrence seems, however, to be a slight increase in the volume of the right half of the heart during inspiration and a decrease during expiration, while with the left half of the heart, according to LAURELL, the reverse is the case.

[1] Submitted for publication, Dec. 18, 1945.

Another of the findings made in the early days of radiographic research was the decrease in cardiac volume occurring in Valsalva's experiment and the increase in volume which takes place in Müller's experiment. Of the two, the changes in connection with the former experiment have aroused the greater interest. As SCHMIDT pointed out in 1905, a Valsalva experiment is performed almost every time strong muscular exertion takes place. As illustrations of such severe effort he mentions weight-lifting, putting the weight, spear-throwing, high-jumping, and certain wrestling and boxing movements. Of more interest from the clinical point of view is the fact that straining at stool, the expiratory effort in asthmatic attacks, and the expulsive work in labor are all carried out under fairly similar conditions. This opinion, as has been pointed out by LIEDHOLM (1939), is that expressed by all the more recent authors.

Thus, Valsalva's experiment is performed in connection with a large number of physiologic functions, all of which require an intensification of the muscular activity. It is not surprising, therefore, that the effect of this experiment on the circulation should have been a matter of interest to physiologists for many years.

German observers seem to have been fairly generally agreed that an increase in the intrapulmonic pressure can impede the blood flow through compression of the vessels in the pulmonary circulation, the capillaries being the first to be affected. GERHARD (1904) considered he had found evidence in support of this theory when he observed that on inflating the lungs, with the thorax opened, there occurred stasis in the jugular vein and a drop in the pressure in the carotid artery, in the same manner as it can occur when Valsalva's experiment is performed. According to MINKOWSKI, this furnished a proof of the fact that the circulatory changes occurring in Valsalvas' experiment are also in large part due to hampering of the pulmonary circulation and not to a retardation of the return flow to the right half of the heart. Another observer, MORITZ, considered that while there certainly is a lessening of the blood flow to the thorax, there must in addition be greatly increased resistance in the pulmonary circulation, which in its turn increases the work of the right ventricle. The view that there is a check to the blood flow in the pulmonary circulation when the intrathoracic pressure is increased was also shared by BÜRGER.

It would seem to be absolutely correct, that compression of the pulmonary vessels can be produced by increasing the intrapulmonic pressure, if at the same time care is taken not to produce the same increase in pressure in the rest of the thorax. The latter event can occur if the lungs are inflated through the trachea and the thorax has been opened by a surgical intervention. If the intrapulmonic pressure then exceeds the pressure in the capillary vessels of the lung compression of these

vessels ought to result. A check to the blood flow in some segment of the vessels of the pulmonary circulation ought also to occur if a local emphysematous inflation, such as occurs for instance in bronchostenosis, is present in the corresponding area of the lung.

In the case of the intrapulmonic pressure rise occurring during a Valsalva experiment, on the other hand, the conditions are somewhat different. In Valsalva's experiment, the glottis or nose and mouth are closed after a more or less deep inspiration and a forcible expiratory effort is then made against the closed glottis. An increase in pressure which is usually more or less evenly distributed in both thorax and abdominal cavity results. The conditions are complicated, it is true, by the fact that the retractive power of the lungs produces a higher pressure in the lungs than in the pleura. This difference between the intrapulmonic and intrapleural pressures is greater in the position of inspiration than in the expiratory position but it is not altered to any great degree by Valsalva's experiment, since the position of inspiration is retained here despite the fact that an expiratory movement is made. The retractive force of the lungs on the heart must therefore continue to be exerted just as if the thorax remained unmoving in the position of inspiration with the air channels open.

As Olof Nordenfelt pointed out in 1934 and 1937, the chest and abdominal cavity can be regarded as one uniform pressure chamber in Valsalva's test. In this chamber the heart, the whole of the pulmonary circulation, and a large part of the systemic circulation are situated. The increase in pressure occurring during the course of the Valsalva experiment thus affects all of these parts of the circulation more or less to the same degree. An assumption such as that of Gerhard and of Bürger, that the pressure rise in the thorax can produce a primary hindrance in the pulmonary vessels must be regarded as contrary to elementary physical laws, as both the right and the left half of the heart are subjected to the same pressure rise as the whole of the pulmonary circulation. Nordenfelt, in 1934, and Liedholm, in 1939, have both endeavoured to discountenance this theory with regard to obstruction in the pulmonary circulation.

On the whole, to regard the chest and abdominal cavity as one pressure chamber in Valsalva's experiment, would seem to be near the truth. Nordenfelt's measurements of the pressure in oesophagus, stomach, and rectum have demonstrated also that the pressure rise is fairly uniform in Valsalva's test, when the experiment is carried out in a position of deep inspiration. On the other hand, if it is carried out with the chest more or less in the expiratory position, the increase in pressure is occasionally much greater in the abdomen than in the thorax, owing to the work of the diaphragm against the abdominal muscles.

A question of greater uncertainty, on the other hand, is whether a greater pressure increase can be produced in the chest than in the abdomen when a Valsalva experiment is carried out in a position of deep inspiration. NORDENFELT believes that the collapse phenomena with rapidly diminishing blood pressure sometimes observed in connection with Valsalva's experiment are due to the fact that the blood depots of the abdomen do not empty owing to abnormal vagal sensitiveness or to vascular atony. I myself advanced the suggestion in 1940 that these collapse states might be due to the fact that the intrathoracic pressure rise is greater than that occurring in the abdomen. This question still remains open to discussion. Another point to be remembered here is the influence exercised by the shape of the thorax, the position of the diaphragm, the size of the abdominal contents, the tonus of the abdominal muscles, and the respiratory movements, on the return flow from abdomen to chest. These factors have been exhaustively studied by WENCKEBACH and later by LAURELL and BJURE in connection with orthostatic anemia.

In general, it is probably correct, as I stated before, to regard the thoracic and abdominal cavities as one pressure chamber in Valsalva's experiment. The rise in pressure in this chamber causes displacement of a considerable mass of blood from this chest and abdominal pressure chamber to the head, neck and extremities. LIEDHOLM's investigations on the pressure in the cubital vein proved that the venous pressure rises continuously for as long as the patient is able to continue the experiment. The arterial blood pressure, measured in the upper arm, usually shows a swift but transient rise during the first few seconds, and then rapidly drops a few tens of mm. Hg. After this, there is generally a slow rise in the blood pressure for the remainder of the experiment. Thus, there is evidently a withdrawal of the blood from the chest and abdominal pressure chamber, proceeding rapidly to begin with and then more slowly, but continuing during the entire experiment. The increase in the volume of blood thereby produced in the veins of the head, neck and extremities can be seen with the naked eye, at least as far as the superficial vessels are concerned. The simultaneous decrease in the size of the heart and the intrathoracic vessels can be observed by radiography.

Two questions of particular importance are, 1) to what extent does Valsalva's experiment imply increased effort for the heart, and 2) to what degree is the work of the cardiac musculature impeded. NORDENFELT remarks with regard to Valsalva's experiment when carried out as »Bürger's Pressdruckprobe» that with the conditions under which the experiment is usually performed, with the exception of the respiratory standstill, it causes practically no circulatory difficulties of mechanical origin either in the pulmonary circulation or in the vessels of the abdominal viscera, and that no extra effort is demanded of the right half of the heart.

It is in all probability true that in the Valsalva test carried out under ordinary circumstances the heart is not called upon to make any particularly violent effort as the direct result of the pressure rise in the chest and abdominal pressure chamber. But on the other hand the cardiac activity is hampered during the experiment by several factors. LAURELL has pointed out some of these to me. He maintains in the first place that the force of the heart probably diminishes as the oxygen supply in the blood decreases. Also, the smaller amount of blood in the ventricles ought to cause lessening of the cardiac energy, since the shorter the muscle fibres at the opening of the systole the weaker the force they can develop at the contraction. LAURELL has also pointed out that the movement of the atrio-ventricular septum towards the apex is hampered during the experiment owing to the diminished flow of blood to the auricles. When the atrio-ventricular septum moves rapidly towards the apex during systole there is an abnormally strong pressure drop in the auricles, and the expulsive effect must therefore also be decreased. Further, LAURELL states that the movement of the septum in the direction of the apex is also hampered in some measure owing to the fact that the diminished stroke volume is accompanied by less distention and extension of the ascending aorta. As the aorta is attached to the atrio-ventricular septum the latter's excursions towards the apex of the heart will thus be hampered. The reduced flow of blood in the coronary vessels results also in a smaller excursion of the atrio-ventricular junction in the direction of the base, since the intramural arteries of the heart muscle are shortened and emptied during systole and again filled with blood, and lengthened, during diastole. This lengthening process, according to LAURELL, will in all probability be smaller than normal when the blood current is diminished, a circumstance which in its turn hampers the diastolic movement in the direction of the base of the heart. The absence of the circulation-promoting effect of the respiration is also stressed.

The chief motive for the present publication is a paper by NILS WESTERMARK in Acta Radiologica, 1945. Basing his arguments on the decrease in volume of the central branches of the pulmonary artery which can be observed in radiographic studies, WESTERMARK describes a method by which he declares he can determine the blood pressure in the pulmonary artery. By taking a series of radiographs under rising intrabronchial pressure, which is measured with a manometer connected with the respiratory passages, he determines the intrabronchial pressure at which a decrease in volume of the central branches of the pulmonary artery takes place. This particular intrabronchial pressure, he maintains, will be equal to the blood pressure in the pulmonary artery. This assertion, as I shall now endeavour to demonstrate, is hardly in accordance with the facts.

We may assume, to begin with, that the circulation of the blood is functioning in the usual manner with free air channels, and we can call the atmospheric pressure 0. We now increase the intrabronchial pressure with V by making the patient carry out a Valsalva experiment, and we then obtain an approximate pressure rise with V in both chest and abdominal cavity. The result will be an impeded return flow from the veins of neck and extremities while the rate of the current in the intrathoracic and intra-abdominal arteries which carry blood to the same parts of the body will be slightly increased. We thus get a decrease in the mass of blood in the vessels of the chest and abdomen. This volumetric diminution, as was pointed out above, can be seen in radiograms of the heart, pulmonary vessels, and aorta thoracalis. Thus there occurs here lessening in calibre of several vessels with pressures widely differing from one another. The pressure in these vessels is raised primarily through the intrathoracic and intra-abdominal pressure rise, but there must be a difference between the pressure in the arteries mentioned and the pressure in the surrounding tissues so long as the heart is in action and is pumping out blood into the arteries, quite apart from the height of the intrathoracic and intra-abdominal pressure arising during Valsalva's experiment.

If we now turn our attention to the stem and the central branches of the pulmonary artery and call the pressure immediately outside these D, with open air passages and the thorax in the same position as in Valsalva's experiment, the pressure within the pulmonary artery will be $P + D$, if by P we mean the blood pressure component resulting from the muscle work of the right ventricle. P is thus the pressure that would have been present in the pulmonary artery if the pressure on the outside of the artery and the heart had been equal to 0, or the atmospheric pressure. With open air channels, D is analogous to a figure with a negative sign and $P + D$ will thus be usually less than P. If we replace the letters by figures which correspond to the pressure in mm. Hg, where the atmospheric pressure is called 0, we would, for instance, obtain the following: $P + D = 40 + (-10) = 30$, where $P = 40$ and $D = -10$. If Valsalva's experiment is now carried out, and the pressure is raised with V we get a pressure of $D + V$ on the outside of the pulmonary artery. Within the artery, the pressure would be $P + D + V$, if the heart continued to function in the same manner and with the same amount of blood as before. As it is not doing so, however, on account of, among other factors, the diminished blood supply from the extremities, neck and head, we must take it that this pressure component P will not be the same, and we can call it P1. We thus have a pressure within the pulmonary artery which is $P1 + D + V$. Outside the artery, the pressure is $D + V$. The pressure P or P1 can, of course, under no circumstances be determined by being

given the pressure V, which is the intrabronchial pressure measured by WESTERMARK.

Finally, brief mention will be made here of the effect of Valsalva's experiment on oesophageal varices. As SCHATZKI pointed out in 1933, these varices swell in some patients during the Valsalva experiment. In some cases he could observe no change in their size, and in some they became smaller during the test. SCHATZKI thought the increase in size might be due to the impeded flow which, according to BÜRGER and other observers, arises in the pulmonary circulation. In my opinion, the cause of the volumetric increase is not to be sought in this direction. The varices in the oesophagus arising as the result of a check to the return flow in the portal system occur almost without exception in conjunction with a greater or lesser degree of congestive enlargement of the spleen. As has been mentioned above, there is sometimes a greater pressure rise in the abdominal cavity than in the thorax during Valsalva's experiment, owing to the work of the diaphragm against the abdominal muscles. The spleen will thus be exposed to a greater increase in pressure than the varices located in the thorax, and it seems highly probable, therefore, that the varices in the chest would consequently receive an increased supply of blood from the spleen.

SUMMARY

On the basis of the experience at present available the author discusses the pressure conditions within and outside the blood vessels occurring in connection with Valsalva's experiment, with special reference to the vessels of the thorax. He maintains that a recently published method for the determination of the blood pressure in the pulmonary artery with the aid of Valsalva's experiment is based on an incorrect assumption regarding the relation between the intrabronchial pressure and the pressure in the pulmonary artery.

ZUSAMMENFASSUNG

An Hand der heute vorliegenden Erfahrungen bespricht Verf. die beim Valsalva'schen Versuch auftretenden Druckverhältnisse in den Blutgefässen und ausserhalb derselben, besonders im Hinblick auf die Thoraxgefässe. Er ist der Ansicht, dass eine kürzlich veröffentlichte Methode zur Bestimmung des Blutdruckes in der Pulmonalarterie mit Hilfe des Valsalva'schen Versuchs auf einer irrtümlichen Annahme inbezug auf das Verhältnis zwischen dem intrabronchialen Druck und dem Druck in der Pulmonalarterie fusst.

RÉSUMÉ

En se basant sur les expériences dont on dispose aujourd'hui l'auteur discute de la pression qui se produit en dedans et en dehors des vaisseaux sanguins dans l'épreuve de Valsalva, spécialement en ce qui concerne les vaisseaux du thorax. Il maintient qu'une méthode, de publication récente, pour la détermination de la pression sanguine dans l'artère pulmonaire à l'aide de l'épreuve de Valsalva est fondée sur une conception erronée de la relation existant entre la pression intra-bronchique et la pression dans l'artère pulmonaire.

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AUS DER RÖNTGENTHERAPEUTISCHEN ABTEILUNG DES »SÖDERSJUKHUSET», STOCKHOLM
(VORSTAND: DOZENT H. AHLBOM)

ZWEI FÄLLE VON ALLERGIE-ÄHNLICHER REAKTION MIT HÄMORRHAGISCHER DIATHESE IM ANSCHLUSS AN RÖNTGENBEHANDLUNG[1]

von

Harry Mossberg

Über das Vorhandensein einer Röntgenallergie oder Röntgenanaphylaxie ist debattiert worden. Einige Verfasser verneinen das Vorhandensein dieses Zustandes, andere haben derartige beobachtet. In der röntgentherapeutischen Abteilung des »Södersjukhuset» hatten wir während des Jahres 1945 die Gelegenheit zwei Patienten zu beobachten, die nach Röntgenbehandlung eigentümliche Haut- und Blutreaktionen zeigten.

Beim Durchgehen der röntgenologischen Literatur findet man eine nicht unbeträchtliche Anzahl Aufsätze von ungewöhnlichen Haut- und Blutreaktionen nach Röntgenbehandlung. So beschreibt PAUL EPSTEIN 1925 einen Fall von ausgebreiteten Hautblutungen nach der Röntgenbehandlung eines inoperablen Cancer uteri. Der Patient bekam auf jedes ein Vorder- und ein Hinterfeld 1 HED sowie $^1/_8$ HED gegen Portio. Am zwölften Tage nach Abschluss der Behandlung enstanden ausgebreitete Petechien an Rumpf und Extremitäten, die nach kurzer Zeit verschwanden, während die Veränderungen auf den bestrahlten Gebieten bestehen blieben und, wo Hautblutungen vorkamen, tiefgehende Nekrosen enstanden. Gleichzietig mit diesen Veränderungen steigerte sich die Kachexie, und der Patient ging nach 42 Tagen ad mortem. EPSTEIN erklärt die Veränderungen als durch Intoxikation durch Zerfall von Cancergewebe und durch Freimachung von Toxinen innerhalb des bestrahlten Gebietes verursacht. Der Verfasser bezieht sich auf HOLZKNECHT der die gleiche Ansicht haben sollte, betreffend das Ursachsmoment der wenigen bisher beschriebenen Fälle von Röntgenexanthem wie Allgemeinbeschädigung durch lokale Röntgenbestrahlung hervorgerufen. EPSTEIN

[1] Bei der Red. am 29. 1. 1946 eingegangen.

ist der Ansicht, dass eine Thrombopenie nicht die Ursache der ausgebreiteten Hautblutung ist.

DEN HOLD, B. LEVIE und M. STRAUB veröffentlichten 1938 einen operierten Fall von Cancer mammae mit Metastasen in den Brustwirbeln, zwei Lymphosarkomen und einem Testistumor mit Knochenmetastasen, welche alle eine Totalbestrahlung nach MALLET, d. h. grosse Behandlungsfelder den Rumpf umfassend, erhielten. Bei sämtlichen enstand eine starke Verminderung der Leukozyten und Thrombozyten mit gleichzeitiger hämorrhagischer Diathese, die bei der Obduktion bestätigt wurde. (In dem Obduktionsprotokoll ist nichts von Knochenmetastasen erwähnt.) Die Dosen per Behandlungsfeld, in der Regel 4, schwankten zwischen 500 r und 3000 r. Sie versuchten nicht die Ursache zu erklären und stellten keine Hypothese über die Entstehungsart der Veränderungen auf.

K. SCHREINER schildert 1924 einen Fall von Röntgenexanthem, das nach WETTERER sehr selten ist und 1-mal auf 100,000 vorkommen dürfte. Es handelte sich um einen Patienten mit Lichen ruber planus, der eine s. g. »Thymus-Reizbestrahlung» wie bei Psoriasis erhielt. Die bestrahlten Hautgebiete wurden nach 14 Tagen dunkelrot und trocken, und über den ganzen Körper verbreitete sich ein Erythem und an den verschiedenen Stellen bis zu thalergrosse Blasen mit serösem Inhalt. Bereits einen Tag nach abgeschlossener Behandlung enstand Rötung auf den Behandlungsfeldern und 8 Tage später zeigte sich das Erythem, und im Zusammenhang damit hatte der Patient ein ausgesprochenes Jucken. Die Reaktion verschwand nach Dauer einer Woche. Nach einiger Zeit wurde eine Probebestrahlung auf einem Hautgebiet von 5 cm^2 Grösse vorgenommen. Nach 8 Tagen zeigte dieses kleine Hautgebiet dieselbe Reaktion, was der Verfasser als Beweis des direkten Zusammenhanges zwischen der Röntgenbestrahlung und dem Exanthem ansah. Dessen Entstehung erklärt er durch Überempfindlichkeit gegen die Toxine, die bei der Röntgenbehandlung gebildet werden (HOLZKNECHT). Die Veränderungen könnten auch erklärt werden nach BARJOU und ROGIER d. h. durch trophoneurotische Störungen innerhalb des Behandlungsgebietes bei hierfür empfindlichen Individuen. Lichen ruber planus steht nach diesen Verfassern auf neuropatischer Genesis und die trophoneurotischen Störungen würden sich auch in den entferntesten Körperteilen bemerkbar machen können. Es würde sich also um abnorme Reaktionen in den nervösen Endapparaten bei hierzu veranlagten Personen handeln.

B. GIARDINA beschreibt 1935 einen Fall, wo Röntgenbehandlung gegen die Adnexa eines Portiocancers angewandt wurde. Gegen Ende der Behandlung entstand ein urtikarielles Exanthem, das schnell allgemein wurde. Nach 10 Stunden waren alle Hautveränderungen verschwun-

den. Die gleiche Erscheinung widerholte sich alle die fünf Male, die der Patient eine Röntgenbestrahlung erhielt. GIARDINA war der Ansicht, dass die Ursache in einem anaphylaktischen Chok zu suchen sei.

1930 schildert F. BERENSTEIN einen Fall von Erythema exsudativum multiforme, das 6 Wochen nach Beendigung der Bestrahlung auftrat und sich auf Hände, Füsse und Mund lokalisierte. Er war der Meinung, dass eine kapillare Beschädigung die Veränderungen erklären könne.

GUTZEIT (1930) spricht von Idiosynkrasie für Röntgenstrahlen. Nach seiner Meinung kann man das Vorkommen einer derartigen Idiosynkrasie nicht bezweifeln, wenn sie auch zu den allergrössten Seltenheiten gehört. Er hat selbst bei lokaler Behandlung einer Basedowstruma ein flüchtiges makulopapulöses Exanthem beobachtet, das mit hohem Fieber, Erbrechen und einem beeinflussten Allgemeinzustand verbunden war. Er zitiert HOLZKNECHT und KIENBÖCK, die auch ein Röntgenexanthem nach lokaler Röntgenbehandlung gesehen haben. GUTZEIT zitiert ausserdem WETTERER, BARJOU und NOGIER, die Dermatosen von ekzematösem Charakter sowie scarlatinösen und erysipeloiden Hautausschlag mit fieberhaften Allgemeinzustand, welche sie als Idiosynkrasien gegenüber den Röntgenstrahlen aufgefasst hatten, beschrieben haben.

FLASKAMP (1930), welcher BARJOU, HOLZKNECHT, KIENBÖCK, NOGIER, SCHREINER und WETTERER zitiert, hat Exanthem im Zusammenhang mit Röntgenbestrahlungen beobachtet und denkt sich dieses durch Toxinüberschwemmung im Organismus hervorgerufen.

REISNER und BRADA (1933) verneinen das Vorkommen von Röntgenexanthem, weil sie mehrere Fälle mit sicheren Zeichen von stärkstem Eiweisszerfall ohne dass ein derartiges Exanthem auftrat, wahrgenommen hatten. Sie stellten fest, dass Exanthem *nach* einer Röntgenbehandlung aber *nicht zufolge* einer Röntgenbehandlung auftreten kann.

KANTSKY beschreibt 1937 3 Fälle mit atypischen Hautreaktionen nach einer Röntgenbehandlung. Der eine Patient bekam nach Behandlung des Beckens (nach totaler Exstirpation eines Cancer uteri) an dreien der Behandlungsfelder eine Akne rosacea, die gänzlich zurückging. Die Rosacea im Gesicht zeigte während dieser Zeit einen Regress. Der andere Fall bekam während der Behandlung eines Hyperthyreoses urtikariellen Ausschlags, teils spärlichen an den Extremitäten, teils massiven auf den Behandlungsfeldern (Der Patient hatte Neigung zu Urtikaria). Beim dritten Fall handelte es sich um einen hämolytischen Ikterus, der 50 r gegen die Milz auf jedem der 3 Felder erhielt, die nach 3 Wochen ein mässig intensives Erythem zeigten. KANTSKYS Ansicht ist es, dass alle diese Reaktionen auf Summationsschäden zurückzuführen sind.

SYLVIA BRAY (1939) schildert 7 Fälle eines generalisierten papulösen Exanthems nach Röntgenbehandlung, wobei in sämtlichen Fällen die

innersekretorischen Drüsen innerhalb der Behandlungsfelder lagen. Sie glaubt auch, dass die Patienten eine Immunität entwickelten, denn bei einer zweiten Behandlungsserie enstanden keine Exantheme.

SCHATTER (1940) behauptet, dass er nicht so selten auftretende Allgemeinschäden in der Art von Haut- und Gelenkreaktionen von ausgesprochen allergischem Charakter nach Röntgenbehandlung beobachtet hat. In diesen Fällen traten generalisierte erythrodermieähnliche Exantheme und uni- oder multilokulare vorübergehende Gelenkanschwellungen auf. Er meint, dass die allergische Reaktion durch strahlungsbedingten Eiweisszerfall entstanden ist.

1932 beschreibt OTTO STRAUSS 7 Fälle, die sämtlich verhältnismässig kleine Röntgendosen erhielten und die mit kräftigen Hautreaktionen reagierten. Vier derselben bekamen ihre Reaktionen nach Durchleuchtung, respektive Exponierung. Nach seiner Ansicht beruhten diese Reaktionen teils auf starker Empfindlichkeit gegen Röntgenstrahlen teils auf Idiosynkrasie. Er hält diese Idiosynkrasie für eine grosse Seltenheit und meint, dass demzufolge die Mehrzahl der Verfasser ihre Existenz verneint.

STRAUSS bezieht sich auf BELA KELEN, der bei 8.000 Röntgenbehandlungen und 34.000 diagnostischen Untersuchungen keinen einzigen Fall von Idiosynkrasie gefunden hat, zitiert aber anderseits FORMAT, FOVEAUX de CORMELLES, MAC KEE, SOILAND, TONSEY, LEVY-DORN und BUCKY als Vertreter der Auffassung, dass eine Idiosynkrasie existiert.

PALTRINIERI (1934) ist der Ansicht, dass es eine Röntgenallergie gibt, und beschreibt 8 Fälle, die früher grosse Dosen von Röntgen verhältnismässig weichen Charakters ein oder mehrere Male erhalten hatten und die stürmische Haut- und Schleimhautreaktionen während oder unmittelbar nach einer Radiumbehandlung in kleinen Dosen gezeigt hatten. Einer der Fälle zeigte ausser örtlicher Reaktion ein Exanthem im Nacken und auf dem Rücken. Er meint, dass die Haut- und Schleimhautreaktionen durch örtliche Allergie bedingt werden und dass die Ungleichheit in der biologischen Wirkung der Radium- und Röntgenstrahlen die Ursache des allergischen Effektes sei.

A. FRANK beschreibt 1935 einen Fall von Überempfindlichkeit in der Haut bei einem Patienten mit subakuter Myeloblastenleukämie. Nach nur 100 r enstand eine kaffeebraune Pigmentierung.

REICH (1935) berichtet von 3 Fällen mit starker Hautreaktion nach kleinen Röntgen-Dosen und meint, dass die Ursache in einer Vasoneurose zu suchen sei.

ALBERT SOILAND (1926) meint, dass es eine Strahlenidiosynkrasie gibt, vergleichbar mit gewöhnlicher Allergie (Hautallergie etc.). Ausserdem gibt es teils eine Allergie bei einer einzelnen Dose mit stärkerer Reaktion als normal, teils eine späte Allergie bei gewissen Personen, die

in späten Röntgenschäden zum Ausdruck kommt und nach mehreren Jahren auftritt.

GROEDEL und KAHL (1926) verneinen das Vorkommen von Idiosynkrasie gegen Röntgenstrahlen.

P. LAZARUS (1926) beschreibt in seinem Handbuch betreffs der biologischen Wirkung der Röntgenstrahlen auf Blut, Lymphe und die blutbildenden Organe, dass bei starker Bestrahlung Thrombopenie, hämorrhagische Diathese, Intoxikation durch Strahlenzerfallsprodukte, Acidos (Röntgenkater), Herabsetzung der Blutviskosität und vermehrte Infektionsgefahr auftreten. Die Strahlenempfindlichkeit betreffend kan man fünf verschiedene Gruppen unterscheiden, u. a. eine Überempfindlichkeitsgruppe, wo er u. a. von Strahlenidiosynkrasie spricht.

Betreffend die Strahlenwirkung auf die Thrombozyten bezieht sich LAZARUS auf MILCHNER und MOSSE, die nach Bestrahlung gefunden haben, dass die Anzahl der Thrombozyten unverändert blieb. KRAUSE und ZIEGLER fanden manchmal eine leichte Verminderung. Nach DUKE (1915) vermindert sich die Anzahl der Thrombozyten bei intensiver Bestrahlung und vermehrt sich bei kleinen schwachen Dosen.

Bei Kaninchen tritt am dritten Tage nach der Röntgenbehandlung eine maximale Senkung der Thrombozytenanzahl ein, welche jedoch wieder kompensiert wird. Die Verminderung der Thrombozyten dürfte eine Folge der Zerstörung der Megakaryozyten sein, die nach WRIGT Mutterzellen der Thrombozyten sind. Gleichlaufend mit der Thrombozytenverminderung geht die Koagulationsfähigkeit des Blutes, d. h. die Koagulationszeit wird verlängert.

Nach HELBER und LINSER (1905), die von LAZARUS zitiert werden, dürften bei Totalbestrahlung von Kaninchen mit hohen Dosen eine herabgesetzte Koagulationsfähigkeit entstehen und fleckförmige Blutungen auftreten.

Betreffend die Thrombozyten schreibt LAZARUS, dass sie sehr widerstandsfähig gegen die Röntgenstrahlen sind. Sie vermindern sich an Anzahl nur nach grossen Dosen, besonders grossen Volumdosen. Dies hat man vor allem bei Tierexperimenten nach Allgemeinbestrahlung oder Injektion von radioaktiver Substanz beobachtet, selten bei Menschen nach intensiver Bestrahlung.

Bei Menschen treten in der Regel keine typischen Veränderungen in der Thrombozytenanzahl bei gewöhnlichen Röntgen- oder Radiumdosen auf. Nach RISSE dürfte bei mittelgrossen und grossen Röntgendosen gleichzeitig mit Verlängerung der Koagulationszeit eine starke Verminderung der Thrombozyten stattfinden. Bei thrombopener Purpura dürfte nach GUGGENHEIM eine Vermehrung der Thrombozyten durch Reizungsdosen an den flachen Knochen eintreten.

HERZGER hat vergeblich versucht eine Röntgenanaphylaxie hervor-

zurufen. Ebenso blieben NIEDERHOFFS Versuche betreffend die Anaphylaxie bei ultravioletten Strahlen (zitiert nach LAZARUS) ohne Resultat.

In dem ersten Falle gilt es einen 62-jährigen Mann, der wegen Myasthenia gravis eine Röntgenbehandlung vorn auf einem Thorax-felde der Ausbreitung des Thymus entsprechend, erhielt. Er bekam 8 Tage lang 3,200 r in Dosen von 400 r pro Behandlung (Feldgrösse 100 cm², 170 kV, 15 mA, 40 cm FHA, Filter ½ mm Cu + 1 mm Al). Am selben Tag, als die Behandlung abgeschlossen wurde (15. 3. 45), begannen grössere und kleinere Hautblutungen an den Armen und hier und da am Körper aufzutreten. Ausserdem bekam der Patient einen sanguinolenten Auswurf. Nach einer Woche begann eine Rückbildung der Hautblutungen und bei der Ausschreibung, 13 Tage nach Abschluss der Behandlung, waren nur noch einige kleinere Reste zurückgeblieben. Die Anzahl der Thrombozyten war während der Zeit vom 19. 3—26. 3 niedrig und hielt sich zwischen 23,000 und 79,000. Die Anzahl der roten Blutkörperchen hielt sich auf ungefähr 3.8 mill., Hb auf ungefähr 65—70 %, und die Anzahl der weissen Blutkörperchen schwankte zwischen 4,000 und 5,000.

Am 14. 4 war die Haut über den Behandlungsfeldern stark gerötet und angeschwollen. Keine Schuppung und kein nässendes Epidermit wurden vorgefunden. Am 16. 4 hatten die Hautblutungen wieder zugenommen und der Patient wurde deswegen am 26. 4 wieder in das Krankenhaus aufgenommen und zeigte da ausgebreitete kleinere Hautblutungen auf beiden Unterarmen, den Handrücken, eine Hautblutung auf der Dorsalseite des linken Unterarms von der Grösse einer Kinderhandfläche sowie kleinere Hautblutungen über die beiden Deltoideusregionen, in beiden Kniebeugen und längs der Cristae iliacae. An den Unterarmen und den Volarseiten der Handwurzeln wurden stecknadelkopfgrosse Petechien und Pigmentierungen wahrgenommen. An den Lungen hörte man in der rechten Flanke einige Rhonchi sonori. Im übrigen nichts Bemerkenswertes von den inneren Organen. Die Anzahl der Thrombozyten war am 27. 4 69,000 und am 28. 4 87,000. Am selben Tage war die Blutungszeit 30 Minuten und die Koagulationszeit 3½ Minuten. Nachher nahmen die Hautblutungen an Ausbreitung bis zum 24. 5 zu. Die Anzahl der Thrombozyten belief sich vom 30. 4 ab im allgemeinen auf über 150,000, selten unter 120,000, oft kam sie bis nahe an 200,000 und darüber.

Die Blutungszeit besserte sich allmählich und währte also am 18. 5 28 Minuten mit einem Prothrombinindex von 96. Am 2. 6 war die Blutungszeit zuf 25 Minuten, am 15. 6 auf 25 Minuten und am 29. 6 auf 3½ Minuten gesunken (normaler Wert). Die Anzahl der roten Blutkörperchen hielt sich auf ungefähr 2.5—3.0 Millionen. HB auf zwischen 60 u. 70 %. Die Anzahl der weissen Blutkörperchen schwankte zwischen 3,000 u. 5,000.

Am 29. 6 war, wie aus obigem hervorgeht, die Blutungszeit normal und der Allgemeinzustand besser. Am 10. 7 befand sich der Patient seit einigen Tagen schlechter und hatte Schluckbeschwerden; ein Teil der Speise ging in die Trachea hinunter. Am 13. 7 verschlimmerte sich der Zustand des Patienten schnell mit Tachykardie, starker Dyspnoe und wurde er in den Tracheen und Bronchien sehr durch reichlichen leicht bluttingierten und zähen Auswurf belästigt. Trotz starker Stimulation ging er am selbigen Tage zugrunde.

WR im Blut, MBR und MKR negativ.

Therapie: Intravenöse Zufuhr von C-Vitaminen, perorale Medikation von Eisen, ausserdem Injektionen von K-Vitaminen (täglich je 1 ml.) 8. 6—13. 6 und zuletzt Bluttranfusion am 24. 5 und 6. 6.

Die Obduktion zeigte Myasthenia gravis? + Cardioarteriosclerosis gravis + Hyperplasia lgl. mediastini + Emphysema pulm. + Diverticulitis coli.

Beim zweiten Fall handelte es sich um eine 75-jährige Frau, die eine Röntgenbehandlung wegen Cancer oesophagi erhielt, der in der Höhe mit der Bifurcatio trachealis lokalisiert war. Sie wurde am 7. 8 in die röntgentherapeutische Abteilung aufgenommen und die Behandlung begann am 9. 8 auf 6 Feldern, 3 vorderen und 3 hinteren, jedes in der Grösse von 100 cm². Auf diesen Feldern erhielt sie alles in allem 11,400 r während 25 Tage mit 600 r in jeder Dose. (170 kV, 15 mA, 60 FHA, Filter $^1/_2$ mm Cu + 1 mm Al). Auf jedem Felde erhielt die Patientin 1,800 r, ausser auf einem Felde, wo sie 2,400 r bekam. Anfangs hielt die Patientin die Behandlung gut aus, fühlte sich jedoch nach einem Monat so müde, dass die Behandlung am 4. 9 abgebrochen werden musste.

Am 10. 9 bekam die Patientin ein universelles urtikarielles Exanthem mit starker Cyanose und Jucken und etwas Ödem in den Lippen und an den Augenlidern. Die Veränderungen waren am ausgesprochensten auf dem Thorax, also in der Umgebung der Behandlungsfelder und auf Nasenrücken, Backen, Ohren und Ellenbogen. Die Hautreaktion auf den Behandlungsfeldern war sehr lebhaft mit Schuppenbildung und beginnender Epithelablösung sowie ausgesprochener Cyanose. Am folgenden Tage mehrten sich die urtikariellen Ausschläge, und Petechien begannen auf den cyanotischen Umgebungen hervorzutreten. Gleichzeitig trat Ödem an Händen und Fingern auf. Am Nachmittag desselben Tages befanden sich die urtikariellen Veränderungen und das Jucken auf dem Rückgang und waren am 12. 9 ganz verschwunden. Dagegen mehrte sich die Anzahl der Petechien und die Cyanose auf der Haut immerfort; in der Mundschleimhaut fand man ebenfalls derartige Veränderungen sowie apthöse Wunden. Am 14. 9 verminderte sich die Cyanose. Die Patientin hustete seit dem 11. 9, bekam allmählich Auswurf und am 13. 9 wurde dieser sanguinolent und gleichzeitig bekam sie leichten, blutigen Fluss aus der Vagina. Am folgenden Tag hatten die Hautblutungen weiter zugenommen und befanden sich jetzt an dem ganzen Körper, am dichtesten um die Behandlungsfelder herum sowie auf dem unteren Teil des Bauches und an den Lenden. Auf den Lungen hörte man zahlreiche Rasselgeräusche. Die Patientin starb am 17. 9 unter dem Bilde einer diffusen Bronchitis.

Der Blutstatus war bei der Aufnahme folgender: Hb 72 %, rote Blutkörperchen 4.39 Millionen, weisse Blutkörperchen 3,000. Diese Werte hielten sich während des Aufenthaltes im Krankenhasue in der Hauptsache unverändert. Die Anzahl der Thrombozyten war am 12. 9 120,000, am 13. 9 156,000 und am 17.9 98,000.

Am 14. 9 war der Prothrombinindex 174, die Blutungszeit 2,5 Minuten, die Koagulationszeit 2.5 Minuten nach Howell-Gram, der Blutkalk zeigte einen Wert von 8.4 mg %. Hess Staseprobe war negativ, die Koagelretraktion normal. Am 17. 9 war der Prothrombinindex bis auf 71 herabgesunken. Die Blutungszeit war am 18. 9 $2^1/_4$ Minuten.

Die Patientin bekam C-Vitaminen während des ganzen Aufenthalts im Krankenhaus, vom 14. 9 ab auch intravenöse Zufuhr von Calcium.

Die Sektion zeigte einen Cancer oesophagi (mikroskopische Untersuchung: undifferentzierten, kleinzelligen, an Bindegewebe reichen Krebs mit Zeichen von Strahleneinwirkung) + Bronchitis mucopurulenta diffusa + Purpura + Marasmus.

Diese beiden Fälle erhielten eine Röntgenbehandlung gegen Mediastinum (oberen, respektive mittleren Teil) und in beiden Fällen trat ungefähr am Ende der Behandlung eine hämorrhagische Diathese mit ausgebreiteten Hautblutungen sowie Blutungen aus den Schleimhäuten ein. In dem zweiten Falle ging der hämorrhagischen Diathese ein akutes ausgebreitetes urtikarielles Exanthem voraus, also ein Zeichen von Allergie. Die Röntgenbehandlung muss als die auslösende Ursache angesehen werden, obgleich es schwer zu erklären ist, auf welche Weise die

Röntgenstrahlen die hämorrhagische Diathese hervorgerufen haben. Es ist wohl anzunehmen, dass es sich um eine lokale Strahleneinwirkung auf das Knochenmark, in beiden Fällen auf das im Sternum und in dem zweiten Falle auch auf das in den Brustwirbeln, handelt, welche die Entstehung irgend eines toxischen Produktes veranlasst hat, das wiederum auf die Thrombozytenbildung eingewirkt hat und dadurch die hämorrhagische Diathese hervorgerufen hat. Die von mir zitierten fünf Fälle von hämorrhagischer Diathese (P. Epstein und Den Hold, B. Levie, M. Straub) bekamen ebenfalls eine Behandlung auf dem Rumpf, d. h. auf einem roten Knochenmark enthaltenden Skelettabschnitt, ein Verhalten, das diese meine Annahme bekräftigt.

Es ist unwiderleglich am leichtesten sich eine derartige Einwirkung als allergisch bedingt vorzustellen. Der Umstand, dass man häufig bedeutend grössere Gebiete mit Knochenmark mit bedeutend höheren Röntgendosen als in diesen Fällen bestrahlt, dürfte ja darauf hinweisen, dass in den zwei beschriebenen Fällen wirklich eine Überempfindlichkeit vorgelegen hat. Das Vorkommen einer Urtikaria in dem einen Falle, wie auch die in diesem Falle besonders lebhafte Hautreaktion auf den Behandlungsfeldern (nur 1,800 r während einer Zeit von 15 Tagen) bestätigt noch mehr diese Annahme.

Nach der Literatur zu urteilen, ist es offenbar, dass eine derartige Überempfindlichkeit sehr selten sein muss, besonders die Form, die mit hämorrhagischer Diathese und Thrombopenie verläuft.

ZUSAMMENFASSUNG

Nach Durchgang der Literatur schildert der Verfasser 2 Fälle von hämorrhagischer Diatese im Anschluss an Röntgenbehandlung, nämlich nach Bestrahlung einer Myastenia gravis (Behandlung des Thymus) und nach Bestrahlung eines Cancer oesophagi. Der Verfasser ist der Ansicht, dass die hämorrhagische Diatese allergisch bedingt ist, und diskutiert ihre Entstehungsart.

SUMMARY

After having perused the special literature, the author describes two cases of hemorrhagic diathesis connected with roentgen treatment viz. after irradiation of a myasthenia gravis (treatment of the tymus) and after irradiation of a cancer in the oesophagus. The author is of the opinion that the hemorrhagic diathesis is due to allergia and he discusses the way in which it arises.

RÉSUMÉ

Après une revue de la bibliographie l'auteur décrit deux cas de diathèse hémorrhagique à la suite de traitements par les Rayons Roentgen, dont l'un s'était adressé à une myasthénie grave (traitement du thymus), l'autre à un cancer de l'oesophage. Il est d'avis que la diathèse hémorrhagique est de nature allergique, et il discute de son mode de production.

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FROM THE ROENTGEN DEPARTMENT OF CENTRALLASARETTET AT BORÅS
(HEAD: DR ERIC HAGBERG)

FRACTURES IN THE ELBOW WITH PARTICULAR REGARD TO THE DISTAL HUMERUS END[1]

by

Bengt A. Nohrman

A survey

All the patients subjected to fractures in the elbow and admitted to the Roentgen Department of Centrallasarettet at Borås during the period of 1932—1941 were after-examined in the Autumn of 1943 and in the Spring of 1944. The observation time did not in any single case fall below two years. The after-examination (A.-E.) comprised, in addition to the usual clinical examination, also roentgen photography of both the elbow joints.

The material consists of 324 persons, representing 328 fractures (four having sustained two fractures at intervals of 3—7 years). A good 80 per cent of the injured persons appeared at the A.-E. Among those who failed to make an appearance, 13 were due to unknown reasons, another 13 were dead and 35 reported that they were prevented from coming.

The fractures have in the great majority of cases involved the distal end of the humerus (*i. e.* 61 per cent). Next in frequency come the radius fractures (collum and capitulum radii), representing almost a fourth of the total number of cases. The ulnar fractures comprise 10 per cent, while two of the bones of the joint were fractured in 6 per cent. In 13 per cent of the cases, the fracture was combined with luxation which, absolutely as well as relatively, is most common among fractures of the humerus.

In the following table the injuries have been divided into two groups according to whether they have occurred in individuals with open (termed »children») or with closed epiphyseal lines (termed »adults»). The mean age of each separate group has been calculated. The cases where two of the bones of the elbow have been fractured have been defined as »combined» cases. The mean age of all the male individuals is 15 years, that of all the females being 25.5 years.

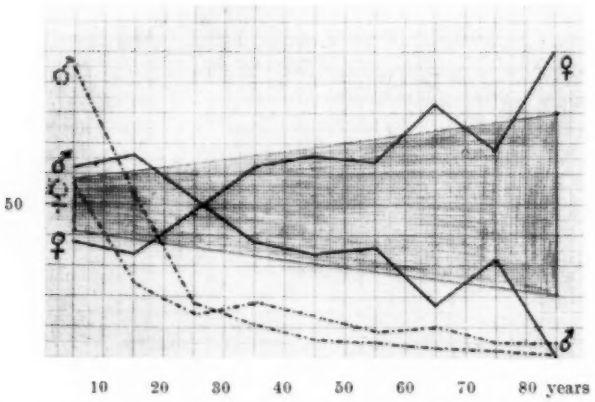
[1] Submitted for publication, Febr. 11, 1946.

Table I.

	Adults	Children	Difference		Mean age	
					Adults	Children
Supracondylar fr.	7 %	42 %	s.	s.	51	6
Other humerus fr.	25 »	59 »	not s.		34	9
Ulnar fr.	19 »	4 »	s.		35	8
Collum radii fr.	6 »	8 »	not s.	s.	35	9
Capit. radii fr.	39 »	—	s.		34	—
Combined fr.	4 »	7 »	not s.		49	10
Sum of fractures	136	192				

It will be seen from Table 1 that the injuries were sustained by adults in 136 cases, or 41 per cent, and by children in 192 cases, or 59 per cent, *i. e.* the difference is statistically significant. Further, it appears that the supracondylar fractures, as well as the humerus fractures, are generally most common in children. The mean age of the supracondylar fractures is the lowest among the children and the highest among the adults. Radius and ulnar fractures, however, are most frequent among adults. Accordingly, fractures through the capitulum radii occur, in the present material, in no single case in individuals with open epiphysis sutures.

As regards the sex distribution, the preponderance of the male sex is statistically significant, representing 56 ± 2.7 per cent, while 44 per cent are females. However, when the frequency between the sexes in each age group of 10 years is studied, the frequency of fractures will be found to be greatest in the lower ages among male persons, but in



The dotted lines denote the total number of fractures. The continuous lines the distribution per cent between the sexes. The difference is uncertain in the shaded area.

the higher ages among females. The frequency differences are partly significant (See the curve).

In 41 ± 2.7 per cent, the injury concerned the right arm, the left arm being affected in 59 ± 2.7 per cent. The difference is significant.

Fractures of the distal humerus end

In order to be able to study the prognosis, the results of treatment must be classified. To find a formula covering both the subjective troubles of the patient and the objective observations at the after-examination is hardly feasible. In the following, the results have been computed in three groups, defined »normal», »satisfactory» and »unsatisfactory». Thus, the definitions do not lay any claim to an adequate illustration of the possible inconveniences suffered by the examined person. However, the agreement among the majority of the cases is fairly good.

The cases where function and configuration is equal in both the elbows have been denoted as »normal». The term »satisfactory» has been applied to cases with a maximum of 20 degrees of reduction in flexion-extension or (and) pronation-supination, with or without a deviation of the carrying angle of, at the most, 10 degrees. None of the cases belonging to this group have reported any noteworthy inconvenience from their injured joint. The remaining cases have been classified as »unsatisfactory».

Supracondylar fractures. The typical fracture occurs just proximal of the condyles, usually at the point where the distal humerus end has a volar angle (this angle will be referred to as »the distal humerus angle»). In cases of the dicondylar variant, the fracture passes a little further distally through the condyles themselves.

The line of the fracture runs in typical cases from the volar surface of the bone in a dorsal-proximal direction. The dislocation takes place in the majority of cases in the same direction (extension fractures). However, in a smaller number of cases the dislocation has a volar direction (flexion fractures).

The supracondylar fractures comprise 78 of the extension type and 13 of the flexion type, *i. e.* in all hardly a third of the total material. Not one of these cases was combined with luxation or fracture of any of the other two bones of the elbow. Among the extension fractures, 75 concerned children and 3 adults, while as regards the flexion fractures the numbers were 5 and 8, respectively. Thus, the former type is incomparably more frequent among children than among adults. As to the latter type, the figures are too low to permit the drawing of conclusions. However, American physicians state the flexion fracture to be definitely more common at a grown-up age.

Table II.

		Normal	Satisfactory	Unsatisfactory
No dislocation	children	41 ± 6 %	10.6 ± 3.8 %	1.5 ± 1.5 %
	adults	30 ± 15 »	30 ± 15 »	—
Remaining dislocation..	children	13.6 ± 4.2 »	27.3 ± 5.5 »	6 ± 2.9 »
	adults	10 ± 10 »	30 ± 15 »	—

Unsatisfactory:

No. 67, boy, 8 years, injury 15 days old. Op. Callus luxurians. — Cub. valg. 20 degrees. Flexion-extension 180—40 and 165—70 degrees, resp.

No. 130, boy, 9 years. Op. twice without satisfactory results. — Flexion-extension 180—40 and 160—65 degrees resp.

No. 241, boy, 7 years. Op. but the fragments slipped in the plaster cast. — Cub. varus 25 degrees. Flex-ext. 180—40 and 130—40 degrees, resp.

No. 286, boy, 12 years. Op. without satisfactory results. — Flex-ext. 180—40 and 180—85 degrees, resp.

No. 308, girl, 2 years. Fracture with slight, dorsally open angle. — Osseous anchylosis in the proximal radio-ulnar joint with lost pro- and supination.

An analysis of the results of treatment has been performed with special regard to whether the reduction of the fractures has been exact or not. In the latter case, a dislocatio ad latus has occurred, attaining more than one corticalis breadth and, generally, combined with a change of the distal humerus angle.

Among the 91 fractures belonging to this group, 76 appeared for after-examination. The result is evident from Table II.

The difference in the number of normal elbow joints in children with and without exact reposition is statistically significant. Thus, the prognosis is certainly less favourable when the reduction has been inexact. This definitely contradicts the contention now and then expressed that fractures in children heal with complete return of function even when the reduction has not been particularly exact. At any rate, this does not apply to the supracondylar fractures.

A good 15 per cent of the after-examined supracondylar fractures disclosed a varus position, in one case (no. 241) attaining 25 degrees, in the rest not exceeding 10 degrees. In all these cases, the lateral humerus condyle of the injured arm is larger than in the uninjured arm, while the medial condyles are equally large in both arms. No corresponding d fference in the size of the condyles is ascertainable in the hardly 10 per cent of cases with cubitus valgus, in one case reaching (no. 67) 20 degrees, while the rest did not exceed 10 degrees.

In three cases, a typical radialis paresis was noticed at admission which, however, disappeared very soon after the reposition. At the A.-E. no signs were seen of the paresis. In no single case the healing was com-

plicated by ishaemic contracture or myositis ossificans. In one case a callus luxurians developed with a callus thicker than a centimetre up to the middle part of the humerus diaphysis (see under Table II, case no. 67).

In several instances, the roentgen examination at the A.-E. showed a deformation of the profile of the distal humerus end. A straightening out of the normal angle between the diaphysis and the condyle part is most common, occurring in 4 cases with normal function and in 13 with satisfactory function. In another 12 cases, a flat, s-shaped curve occurs dorsally of the distal humerus end, causing the trochlea and the capitulum humeri either to verge upon or to lie dorsally of a plane through the volar region of the diaphysis. This deformation is, in half the number of cases, combined with normal function, the other half being satisfactory. In three cases of flexion fractures, the distal humerus angle is reduced to 90 degrees, being in all three cases combined with normal function.

Condyle and epicondyle fractures together represent a good third of the total material, or a little more than the supracondylar fractures. In this compilation they are most common in childhood. However, from a statistical point of view, this is not quite significant (the difference = $= 2.8 \times$ the mean error). These fractures are combined with luxation in almost 30 per cent.

Among the injuries of this group, the epicondylar fractures are the most frequent, comprising almost 50 per cent, while the fractures of the lateral condyle only occur in close on 40 per cent, and those of the medial condyle in a good 10 per cent. Out of 33 epicondylar fractures in childhood, 29 have been subjected to after-exam nation, being 16 out of 19 as regards adults. In only two cases was the injury sustained by the lateral epicondyle.

The results of treatment of the epicondylar fractures appear in Table III.

Table III

		Normal	Satisfactory	Unsatisfactory
No dislocation	children	31.1 ± 8.6 %	20.7 ± 7.4 %	—
	adults	43.7 ± 12.5 »	12.5 ± 8.4 »	6.3 ± 5.9 %
Remaining dislocation..	children	24.1 ± 7.9 »	24.1 ± 7.9 »	—
	adults	12.5 ± 8.4 »	25 ± 10.8 »	—

Unsatisfactory:

No. 223, male, 18 years. Luxation. Med. epicond. rotated 90 degrees. After 3 weeks, extensive myositis ossif. A.-E.: Ext.-flex. 180—45, 130—55 degrees, respectively.

In 20 of the cases of epicondylar fractures reduced without surgical intervention, the position obtained was not quite exact, the dislocated fragment having slipped a few millimetres, usually in a distal direction. In only four cases (20 per cent), all at a grown-up age, did the bone heal, while in the remaining cases, three of which were adults, a diastasis resembling an epiphyseal line was seen to remain in the roentgen picture even when the real epiphyseal lines had ossified. However, the function of the joint has apparently not been affected. Among seven operated cases, five healed with synostosis.

The fractures through the lateral condyle constitute a somewhat smaller group than the previous one. In childhood, this fracture passes in a typical manner just proximally of the epiphyseal line between the diaphysis and the capitulum humeri. The dislocated fragment will consist of the capitulum humeri, the epiphyseal line and a narrow fragment from the metaphysis. At a grown-up age, the fracture has a more irregular course. The 43 fractures of this group have occurred in children in 75 per cent, and three fourths of them are of the type described above.

Table IV

		Normal		Satisfactory		Unsatisfactory	
		Adults	Children	Adults	Children	Adults	Children
Medial condyle	No dislocation	—	50 ± 16.7 %	—	30 ± 15 %	—	—
	Remaining dislocation	—	—	33 ± 33 %	20 ± 13.3 »	67 ± 33 %	—
Lateral condyle	No dislocation	57.1 ± 20 %	50 ± 10 »	28.6 ± 18 »	19.3 ± 7.7 »	—	—
	Remaining dislocation	—	15.4 ± 7 »	—	3.8 ± 3.8 »	14.3 ± 14 »	11.5 ± 6.4 %

Unsatisfactory:

No. 65, female, 22 years. Fr. of med. cond. Extens. myositis ossif. A.-E.: Ext.-flex. 180—45, 105—60 degrees. Roentgen: Large exostoses, as remnants after the myositis.

No. 302, female, 56 years. Fr. of med. cond. Op. without satisfactory results. A.-E.: Ext.-flex 180—40, 130—55 degrees.

No. 95, female, 58 years. Lat. cond. crushed into several fragments. Op. A.-E.: 180—35, 125—65 degrees.

No. 170, male, 10 years. Lux. Op. 13 days after the injury without satisfactory results. A.-E.: Cub. varus 35 degrees. Ext.-flex. 180—40, 180—65 degrees.

No. 233, male, 5 years. Injury seven weeks old. Op. without satisfactory results. A.-E.: Cub. valg. 30 degrees. Ext.-flex. 180—35, 180—45 degrees.

No. 255, female, 8 years. The fragment slipped in the plaster Op. eight weeks after injury without satisfactory results. A.-E.: Ext.-flex. 180—35, 150—35. Roentgen: Greatly deformed joint.

Also the fractures through the medial condyle have a typical appearance in individuals where the epiphysis-lines have not ossified. Thus, the fracture proceeds from a point just proximal of the spot of the medial epicondyle to the middle point of the epiphyseal line between the capitulum and the diaphysis humeri. This type is represented among all ten cases in this material of fractures through the medial condyle in children. In three cases in adults, the fractures have a more longitudinal direction in the arm. All the fractures are of the extension type.

The results of treatment are illustrated in Table IV.

Myositis ossificans was seen in six of the fractures of this group. Three of these were epicondylar (two dislocated) and three condylar fractures (one dislocated). In one case of every type the function was unsatisfactory, most probably depending on the earlier myositis, because as remnants after this there were seen large exostoses on the humerus, and the limitation of the function of the joint was, at least partly, caused by the exostoses.

SUMMARY

328 elbow fractures have been examined. In accordance with earlier observation, the humerus fractures are most common in childhood, while the radius and ulna fractures are most frequently sustained by adults. Male individuals and the left arm are more often affected than females and the right arm. The prognosis of the humerus fractures included in the present material indicates that an exact reduction is of vital importance also in children.

ZUSAMMENFASSUNG

Verfasser nach-untersuchte 328 Patienten mit Frakturen im Ellenbogengelenk. Das untersuchte Material bestätigt wiederholt dass die Humerusfrakturen gewöhnlich bei Kindern vorkommen, im Gegensatz zu den Radius- und Ulnafrakturen, die meist bei Erwachsenen anzutreffen sind. Das männliche Geschlecht sowie der linke Arm sind öfter befallen als das weibliche Geschlecht und der rechte Arm. Die Prognose, auch für das Kindesalter, hängt mit der Sorgfältigkeit und Genauheit der Reposition nahe zusammen.

RÉSUMÉ

L'auteur a examiné 328 cas de fractures de l'articulation cubital. Conformément aux observations faites jusqu'ici l'auteur constate que les fractures du humerus se retrouvent d'habitude chez les enfants, tandis que parmis les adultes les fractures radiales et ulnaires sont plus fréquentes. Le sexe masculin ainsi que le bras gauche sont atteints plus souvent que le sexe feminin et le bras droit. Le pronostic d'après le matériel examiné demontre que la reposition exacte est de plus grande importance également chez les enfants.

FROM THE RADIOPHYSICAL INSTITUTE OF KAROLINSKA SJUKHUSET, STOCKHOLM (CHIEF: PROF. R. SIEVERT) AND THE II. MED. CLINIC OF SÖDERSJUKHUSET, STOCKHOLM (CHIEF: PROF. J. TILLGREN)

BLOOD CHANGES IN RADIOLOGIC WORK[1]

by

Nils G. Nordenson

The present study is an attempt to gain a conception of the deleterious effect incidental to radiologic work and therewith obtain an exact basis for estimating risks involved in the same. Eventual blood changes among the personnel engaged in the work have served as an aid.

Changes of the red and white blood pictures are comprised in the study but thrombocytopenic changes will not be touched upon.

A competent estimation of eventual changes in the peripheral blood picture with the application of roentgen rays and radium demands a complete knowledge of the quantitative and qualitative conditions of the blood.

The material acquired in yearly investigations of persons engaged in radiologic work (R-material) cannot be directly compared with average values. It is necessary to get a conception of the normal variations from individuals who work under similar conditions, that is to say, hospital personnel. Age differences are eliminated also for the most part by selecting such a material. For this reason I procured a material consisting of 250 women and 200 men. All the women have had their work in hospitals but of the men only 130, the remainder being voluntary blood donors at Stockholm City's blood-giving central. They were all healthy and of the same range of age. The letter N indicates this material in the following.

Comments on the variations of the blood pictures in the N-material. The results are collocated in the Tables and Curves I—IX.

In an unexceptionable normal material the *hemoglobin* varies from 80 % to 110 % among men and among women from 75 % to 100 %. The number of *red blood corpuscles* differs among men and women and ranges between 4.0 and 6.0 for the former and 3.4 and 5.0 mill. for the latter.

In my N-material about 85 % of the values for hemoglobin are between 81 % and 100 % for men. 7 % and 8 % of the values respectively are

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below 80 % and above 100 %. The lowest value comprised 67 % and the highest 105 % hemoglobin. 85 % of the hemoglobin values ranged between 76 and 90 % for females. About 7 % of the values were below 76 and above 90 % hemoglobin. The minimum and maximum were 66 % and 100 % respectively.

The values for the red blood corpuscles in the N-material amount to 72 % between 4.0 and 5.0 mill. among men. For the erythrocytes 3 % and 25 % of the values were below and above the mentioned limits. The lowest value was 3.8 and highest 5.8 mill. Among females 76 % of the values were between 4.0 and 5.0 mill. erythrocytes. 21 % and 4 % of the values were below and above the mentioned limits. The variation limit was 3.6—5.1 mill. erythrocytes. Accordingly in the N material there is a tendency towards anemia which, broadly speaking, corresponds to the normal anemia rate among Swedish women. The curves clearly reveal the normal sex difference.

The strict normal variations for the *white blood corpuscles* range between 4,000 and 10,000. By reason of the great daily variations the fasting values would seem to be the most suitable although this assumption has been criticized by various authors (33) (especially in the estimation of the values of leukocytes among the personnel in radiologic departments samples ought to be taken between 11—12 o'cl. instead). At all events with the said limits all the normal variations should be covered.

The values of the N-material are not fasting values. Among the males, 73 % lie between 5,100—8,000 leukocytes while 14 % lie above and below the said limits. 4,800 and 9,600 leukocytes comprised the lower and higher values respectively. Among women 80 % of the leukocyte values are between 5,100 and 8,000 — about 10 % below and above the said values. The minimum and maximum values were 4,600 and 9,400 respectively.

The differential count reproduces the relative distribution of the various types of white blood corpuscles.

The percentage of *rod forms* represents the degree of immaturity of the myeloid cells (= shift to the left). Normally not more than 5 % rod forms occur in the peripheral blood. The N-material reveals that in both sexes 99 % of the values are below 5 %. The conformity with strict normal conditions is accordingly very good.

The *segmented leukocytes* vary under normal conditions between 45 and 65 %, irrespective of sex. In the N-material about 76 % and 80 % of the values are found among men and women respectively within the said limits. Below 45 % and above 65 % segmented cells to 5 % and 9 % are found among males and among females to 4 % and 16 % respectively. The range of variation among the sexes was 40 %—73 % and 35—77 %.

Granulocytopenia (less than 40 % segmented cells) and granulocytosis (more than 65 % segmented) are well correlated to the increase and de-

crease of the *lymphocytes*. The exact normal variation limits for the lymphocytes reported in current handbooks is doubtless too near (26, 29, 33) and this refers especially to the upper limit which is stated to be 28 %. With certainty the lymphocytes have a normal variation range of 22 %—45 %. The range among males in the N-material is from 17 %—50 %. With reference to the values, 81 % lie within the limits of 25 %—45 % lymphocytes: below the lower limit are 17 % and above the upper 2 % of the values. Among the females the variation limits are 13 %—62 % and of the values, 83 % come within the range of 25—45 % lymphocytes: below 25 % are 14 % and above 45 % lymphocytes are 3 % of the values. There is no palpable difference between the sexes in my N-material.

The *eosinophil leukocytes* vary in an unexceptional normal material from 2 %—4 % irrespective of sex. The N-material deviates to the extent that about 65 % of the values among both sexes are under 2 %. 10 % and 6 % of the values among both males and females lie above the 4 % limit. The range of variation in the N-material is 0—7 % for men and 0—10 % for women. The conformity of the *basophil leukocytes* with strict normal conditions is very good. As a matter of fact 100 % of the values in the N-material falls below 1 % of the basophils. The variations for males and females amount to 0—1.5 % and 0—1 % respectively.

The *monocytes* vary in a strict normal material between 6 and 8 %, irrespective of sex. The deviation in the N-material is such that 64 % and 74 % of the values for men and women lie below 6 % monocytes. Among males 20 % and among women 10 % of the values are above 8 % monocytes. The limits of variation in the N-material are 0—17 % and 0—15 % among men and women.

Special attention has been paid to changes in the morphology of the individual cell and *neither hypersegmented leukocytes nor pathologic lymphocytes were revealed in the N-material.*

Literature survey of changes and eventual injuries to the blood and bone-marrow after roentgen or radium irradiation. By reason of the manner of its application radium seems to have a greater tendency to cause more serious changes than roentgen (25, 34, 35).

The severe and often deadly anemias among the radiology pioneers (11, 31) are well-known. The deleterious effect is more pronounced in cases of preformed hemopoietic disturbances (19, 21). The really grave injuries are rare on the whole and at this stage the changes are irreversible.

Investigations with experimental animals show the development from slight changes to those of a more serious nature (3, 6, 30). A first change appears to be leukocytosis (1, 3, 7, 13, 21, 27, 30), increased shift to the left (28), increase of hemoglobin (10, 16, 17, 22), reticulocytosis (15, 16, 17), eosinophilia (3, 4, 6, 15, 17) and basophilia (6). These changes can be

combined in various ways. Granulocytosis corresponds to lymphocytopenia (13, 14, 27). Secondly, leukopenia manifests with or without granulocytopenia (3, 4, 7, 10, 17, 22, 27) and monocytosis (7, 17, 18). After this stage where the changes are reversible as a rule, irreversible injuries with anemia develop as the chief symptom. The severest injuries generally have combined changes (4).

There have been lively discussions as to whether slight changes should be regarded as injuries or not. These discussions appear fruitless to me. The small changes observed are undoubtedly reactive and investigations with experimental animals reveal a distinct chain of developments with transitional phases within each other from the slightest change to grave and real injuries. From a biologic point of view there is nothing remarkable about an agency (in this case irradiation) first giving a reactive change eventually of the hyperfunction type = irritation (direct or indirect), which changes later into hypofunction.

Complete blood impairment is a direct result of diminished bone marrow function and the hypoplastic and aplastic conditions are well-known (11, 32, 33, 34, 35). The reaction of the bone marrow to direct irradiation has been excellently illustrated by intravital bone marrow studies (5, 8, 15, 24, 28) which latter eloquently confirm the assertion that irradiation can produce an irritating effect. Increased mitosis and amitosis (15) obtains and the myeloid cells especially, manifest a more speedy maturition (5, 15).

Still another change takes place in the peripheral blood which in all probability is caused by irradiation, namely, the increase in size and hypersegmentation of the leukocytes (24, 28). This change corresponds to a disturbance of the maturation process in the myelopoiesis (24, 28, 33) of the bone marrow which is very characteristic and analogous for instance with the changes in pernicious anemia. The irritating or eventual injurious effect of irradiation cannot be denied in the presence of such evidence.

Differential diagnosis. The hematologic picture is not complete unless the differential diagnostics be briefly touched upon. The manifest changes are reactive and might obviously occur under other conditions. One single injury or change need only constitute an observandum and nothing more. The change will not be pathognomonic before several or all the hematologic symptoms are revealed.

Preventive measures with reference to irradiation injuries. Radium and roentgen work undoubtedly entail many risks which as a rule are kept well under observation. There are special supervisionary organs in many quarters. In England the Roentgen Ray and Radium Protection Committee acts as State organ. How seriously this instrument apprehends the irradiation injury problem is illustrated by the following quotation. »It is better for the worker to have a fortnight's holiday for a small or sus-

picious blood change than to continue with the work and become an invalid for months.» In Germany and France there are corresponding State organs. In Sweden the Radiofysiska Institutionen at Karolinska Sjukhuset is the supervisory authority.

Material comprising blood investigations of the personnel engaged in radiologic work = the R-material. On Dec. 31, 1944 the collective material of the obligatory blood investigations in 1942, 1943 and 1944, stipulated in the Swedish X-ray protection-law (SFS 334 and 640/1941) came to hand. The material includes 1,566 individuals, 458 men and 1,108 women. The total number of registered investigations amounts to about 29,000. The material has been adapted in its entirety and is reproduced in Tables and Curves I—IX.

The material is impaired by almost unavoidable errors. Accordingly, the investigations for natural reasons are not performed by the same person (investigational results are sent in from practically all the radium and roentgen departments in Sweden). As a rule, however, the investigators are doubtless of a qualified class. Moreover, broadly speaking, the material does not differ from well-known and normal conditions. The differential counts for the 1944 year's investigations were for the greatest part computed by the author, when controls were obtained in many cases, and on these occasions no greater deviations were registered. The errors, for the most part, should have been eliminated by reason of the very great number of examinations in every category of the various corpuscular elements of the peripheral blood. The figures amount to about 1,000 among males and 2,000 among females.

Results. All the investigational results are illustrated in Tables and Curves (the thin curve = the N-material, the thick curve = the R-material).

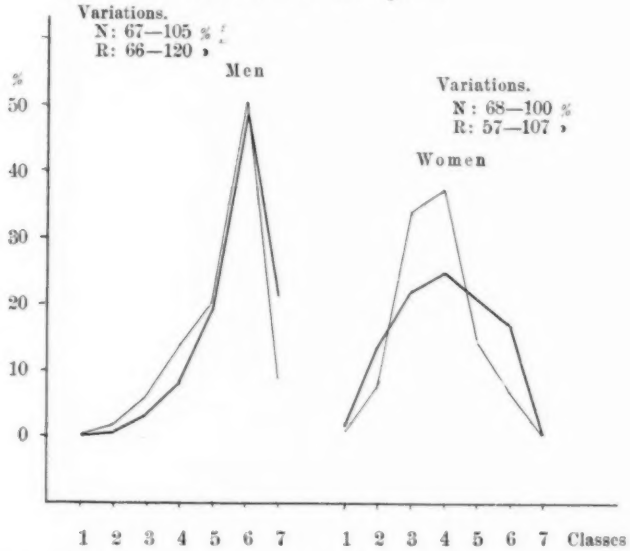
The variations of the *hemoglobin* and *red blood corpuscles* are to be found in Table and Curve I and II. The normal sex difference is distinct as was expected. Among the males there occurs no tendency to anemia but on the other hand an unmistakable propensity to polycythemia — 21 % of the values for the hemoglobin are above 100 % as against 9 % in the N-material. The same applies to the red blood corpuscles. The females tend clearly towards anemia — 14 % of the hemoglobin values are below 75 % as against 7 % in the normal material. 14 % in considerably above the normal anemia tendency of the female sex. No very pronounced traces of polycythemia were revealed among the women. The diminution of the red corpuscles in the female group of the R-material is scarcely noticeable and the same can be said of the polycythemia tendency. The variation limits are greater in the R-material in respect of the hemoglobin, among men 66—120 %, among women 57—107 % also as regards the red blood corpuscles 3.6—6.4 and 3.0—5.7 milj. respectively.

Table I A.

Hemoglobin.

Classes See Curve IB	Hbl %	♂ R		♂ N		♀ R		♀ N	
		Total	%	Total	%	Total	%	Total	%
1	55— 60	—	—	—	—	10	0.5	—	—
	61— 65	—	—	—	—	15	0.7	1	0.4
2	66— 70	2	0.2	1	0.5	80	4.0	2	0.8
	71— 75	6	0.7	2	1.0	192	9.2	16	6.4
3	76— 80	26	2.9	12	6.0	456	21.9	85	34.0
4	81— 85	70	7.8	27	13.5	516	24.8	93	37.2
5	86— 90	174	19.3	40	20.0	429	20.6	36	14.4
6	91—100	435	48.3	101	50.5	351	16.8	17	6.8
7	>100	187	20.8	17	8.5	31	1.5	—	—

Curve I B. *Hemoglobin.*



The variations of the *white blood corpuscles* are reproduced on Table and Curve III. 24 % of the values for the men are below 5,000 leukocytes and 6 % of the values are below 4,000 against 14 % and 0 % in the N-material. Here is a distinct tendency to leukopenia. Moreover there is some propensity to leukocytosis and of the values, 3 % are above 10,000 white blood corpuscles as against 0.5 % in the N-material. A similar circumstance applies to the women. The distribution of the leukocyte values is considerably greater in the R-material where among men it is 2,400—17,400 and among women 2,100—13,600.

Table II A.

Red blood cells.

Classes see Curve IIB	Red cells mill.	♂ R		♂ N		♀ R		♀ N	
		Total	%	Total	%	Total	%	Total	%
1	3.0—3.5	—	—	—	—	40	2.1	—	—
2	3.6—4.0	29	3.6	6	3.0	454	23.3	52	20.8
3	4.1—4.5	203	25.1	30	15.0	910	46.5	135	54.0
4	4.6—5.0	362	44.6	115	57.5	498	25.5	54	21.6
5 . . .	5.1—5.5	186	23.0	47	23.5	43	2.2	9	3.6
	>5.6	30	3.7	2	1.0	7	0.4	—	—

Curve II B. *Red blood cells.*

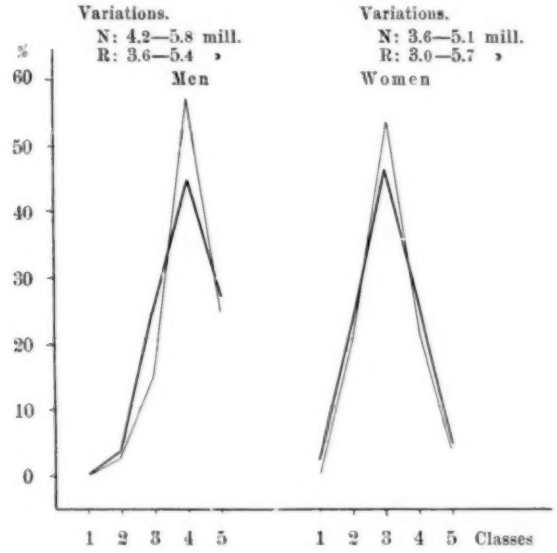


Table and Curve IV represent the variations of the *rod forms*. The tendency to a shift to the left is found very definitely increased in both sexes. Accordingly among males and females respectively, 18 % and 28 % of the values fall above the 5 % rod forms against approx. 1 % in the N-material. Simultaneously there is also a lessening of the »shift to the left». The variation limits are greater in the R-material — among men and women respectively 0—36 % and 0—41 %.

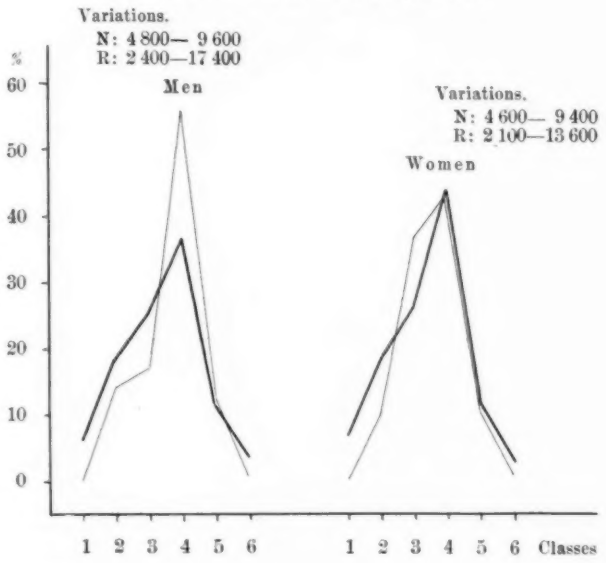
The *segmented leukocytes* (Table and Curve V) reveal a considerable propensity to granulocytopenia. About 20 % of the values for leukocytes are below 45 % against about 4 % in the normal material. There was no

Table III A.

White blood cells.

Classes see Curve IIIB	White cells	♂ R		♂ N		♀ R		♀ N	
		Total	%	Total	%	Total	%	Total	%
1	2 — 3 000	5	0.6	—	—	20	1.0	—	—
	3.1— 4 000	47	5.2	—	—	129	6.5	—	—
2	4.1— 5 000	166	18.1	28	14.0	357	18.1	25	10.0
3	5.1— 6 000	227	25.0	34	17.0	508	26.0	91	36.4
4	6.1— 7 000	196	21.7	85	42.5	423	21.5	61	24.4
	7.1— 8 000	132	14.5	27	13.5	247	12.5	46	18.4
5	8.1— 9 000	72	7.8	14	7.0	142	7.2	17	6.8
	9.1—10 000	37	4.0	11	5.5	87	4.4	9	3.6
6	10.1—15 000	26	3.0	1	0.5	56	2.8	1	0.4
	>15 000	1	0.1	—	—	—	—	—	—

Curve III B. *White blood cells.*



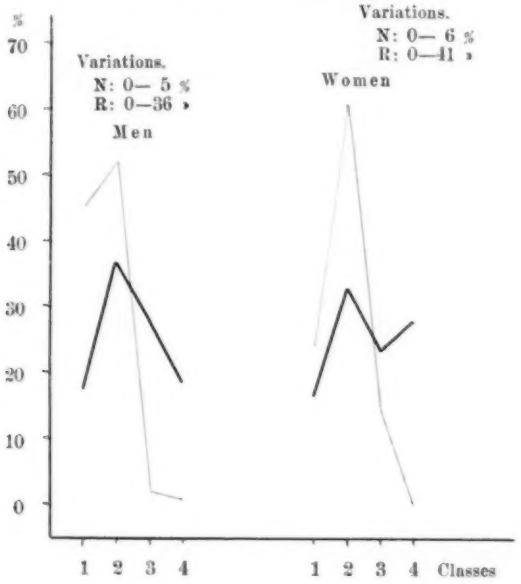
trend towards granulocytosis even though extreme values were registrated. The lymphocytes (Table and Curve VIII) behave to the contrary. Granulocytopenia corresponds to lymphocytosis. 12 % of the values for lymphocytes among males is above 45 % and among females 14 % against only about 2 % for both sexes in the N-material. There was no tendency to lymphocytopenia in the R material. The range of variation for the segmented leukocytes in R material is greater than in the N-material and is

Table IV A.

Rod forms.

Classes see Curve IVB	Rod forms %	♂ R		♂ N		♀ R		♀ N	
		Total	%	Total	%	Total	%	Total	%
1	0 — 0.9	164	17.1	90	45.0	329	16.1	60	24.0
2	1 — 2.9	353	36.8	104	52.0	670	32.8	152	60.8
3	3 — 5.0	268	28.0	4	2.0	473	23.2	37	14.8
4 . . . {	5.1—10	144	15.1	2	1.0	490	24.0	1	0.4
	>11	29	3.0	—	—	79	3.9	—	—

Curve IV B. *Rod forms*



among the men and women respectively 12 %—82 % and 10 %—83 % — the same figures for the lymphocytes amount to 10 %—70 % and 9 %—72% thus greater than in the N-material.

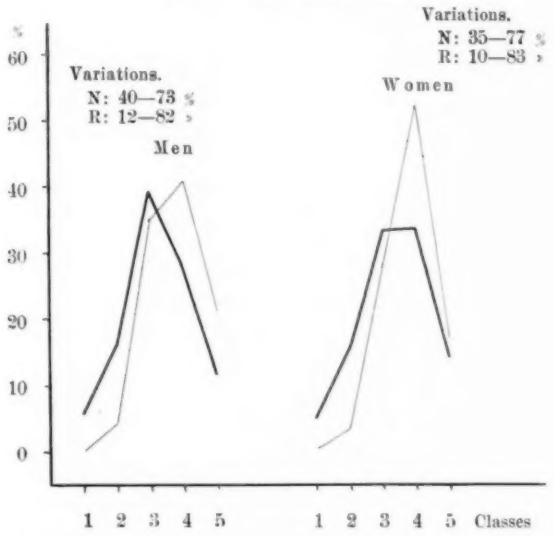
With respect to the *eosinophils* (Table and Curve VI) and basophils (Table and Curve VII) tendency to both is shown by each sex. 14 and 11 % of the values for eosinophils are above 4 % in the R material in respect to both men and women. The figures for the *basophils* are still more marked and are 10 % and 7 % above 1 %. The propensity for the latter is more pronounced among the men than the women but as regards the eosinophils it is the contrary. The variation range for the eosinophils among males

Table V A.

Segmented leukocytes.

Classes see Curve VB	Segmented %	♂ R		♂ N		♀ R		♀ N	
		Total	%	Total	%	Total	%	Total	%
1	<30	21	2.2	—	—	45	2.0	—	—
	31—35	28	3.0	—	—	51	2.3	1	0.4
2	36—40	51	5.4	2	1.0	138	6.1	—	—
	41—45	96	10.4	7	3.5	210	9.3	8	3.2
3	46—50	161	17.4	27	13.5	312	14.0	26	10.4
	51—55	203	22.0	43	21.5	425	19.2	43	17.2
4	56—60	118	12.7	51	25.5	426	19.2	71	28.4
	61—65	142	15.4	32	16.0	314	14.2	59	23.6
5	66—70	73	8	26	13.0	206	9.2	27	10.8
	>70	31	3.5	12	6.0	103	4.5	15	6.0

Curve V B. *Segmented leukocytes.*



and females is 0—17 % and 0—34 % and for basophils the corresponding figures are 0—4 % and 0—4.5 % respectively. Thus the amplitude of the variation is greater than in the N material.

The monocytes (Table and Curve X) in the R material manifest no deviation from the N material. The range of variation is somewhat greater than normally, among men and women respectively it is 0—26 % and 0—31 % against 0—17 % and 0—15 % in the N material.

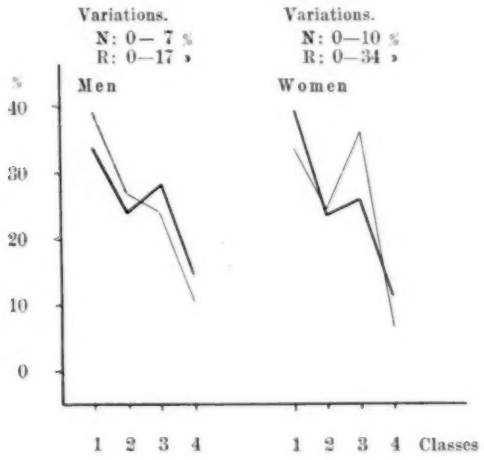
The cellular morphologic changes which were observed in the R ma-

Table VI A.

Eosinophils.

Classes see Curve VIB	Eosinophils %	♂ R		♂ N		♀ R		♀ N	
		Total	%	Total	%	Total	%	Total	%
1	0 —1	343	33.8	78	39.0	869	39.3	84	33.6
2	1.1—2	242	23.6	53	26.5	535	23.7	61	24.4
3	2.1—4	286	28.3	48	24.0	570	25.9	90	36.0
4	>4	145	14.3	21	10.5	246	11.1	15	6.0

Curve VI B. *Eosinophils.*



terial but not in the N material, comprised increase in size and *hypersegmentation* of the leukocytes as well as a *pathologic change of the lymphocytes*. Hypersegmentation is an all too well known phenomenon to need further description. The pathologic lymphocytes are greater than normally and have a loosened nucleus as well as a different plasma stain. To some extent they have the character of reticulum cells.

The total number of observed blood changes per individual (regardless of sex) comprises 822 corresponding to 52 % (see Table X) of the whole R-material.

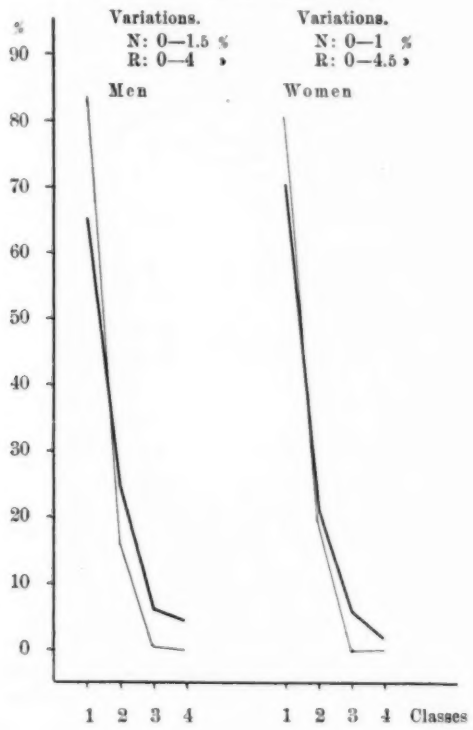
Comments and discussion. In the R-material certain quantitative and qualitative changes have been observed which deviate from the normal. Corresponding changes have been described in the literature. I myself have found a slight tendency to anemia among the female sex and a propensity to polycythemia among both sexes. The white blood corpuscles

Table VII A.

Basophils.

Classes see Curve VIIB	Basophils %	♂ N		♂ N		♀ R		♀ N	
		Total	%	Total	%	Total	%	Total	%
1. . . .	0	674	65.5	167	83.5	1 476	71.0	201	80.4
2. . . .	0.5—1	264	24.9	32	16.0	451	21.2	49	19.6
3. . . .	1.1—2	66	6.1	1	0.5	117	5.9	—	—
4. . . .	>2	46	4.4	—	—	39	1.9	—	—

Curve VII B. *Basophils.*



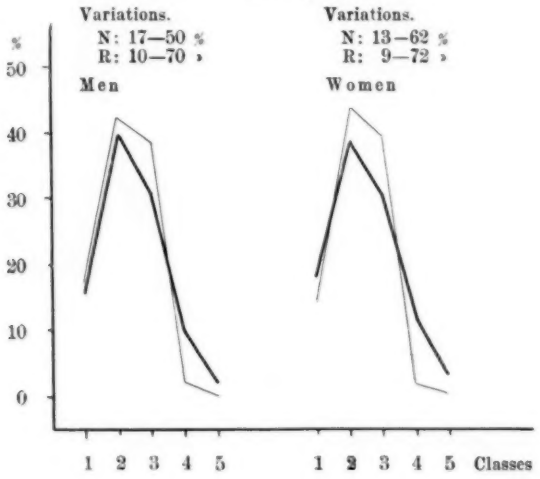
revealed a tendency to leukopenia, less marked with leukocytosis, a considerably increased »shift to the left» and certain eosinophilia and basophilia. The monocytes manifested no changes in contradistinction to the literature reports. Other authors have likewise observed hypersegmentation but not in respect to the pathologic lymphocytes.

Table VIII A.

Lymphocytes.

Classes see Curve VIIIB	Lympho-cytes %	♂ R		♂ N		♀ R		♀ N	
		Total	%	Total	%	Total	%	Total	%
1	>20	37	3·6	8	4.0	111	5.0	7	2.8
	20—25	124	12·2	26	13.0	274	12.6	29	11.6
2	26—30	196	19.2	34	17.0	442	19·8	61	24.4
	31—35	211	20.8	51	25.5	417	18.7	74	29.6
3	36—40	182	17.8	45	22.5	424	19.1	51	20.4
	41—45	144	14.2	32	16.0	250	11.3	22	8.8
4	46—50	63	6.2	3	1.5	150	6.8	3	1.2
	51—55	39	3.8	1	0.5	79	3.6	2	0.8
5	56—60	13	1.3	—	—	49	2.2	—	—
	>60	7	0·9	—	—	20	0.9	1	0.4

Curve VIII B. *Lymphocytes.*



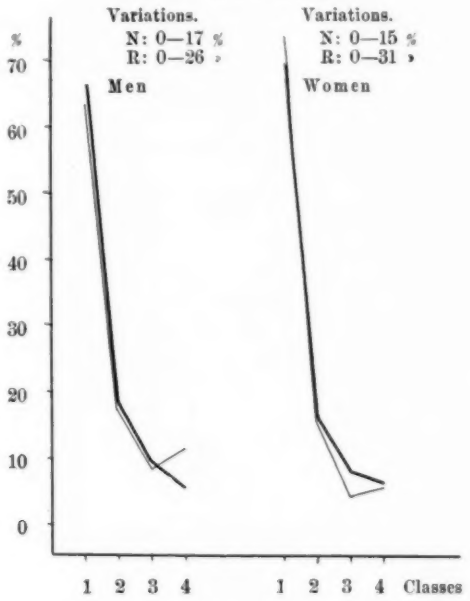
A distribution of the various changes irrespective of sex is reproduced on Table X. The group »combined changes» cannot be more closely analysed, as the material, notwithstanding its size, is of an all too inconsiderable comprehension. The percentage of changes amounted to 52 % which figure appears high in comparison with that reported by Laborde and Leclerq — 31 %. It is impossible to discuss the deviation when the primary material of the authors cannot be studied. Dare one, however, only ascribe the more known changes to the material of these authors (leukopenia, granulocytopenia and anemia), the conformity would be very good — 25 %.

Table IX A.

Monocytes.

Classes see Curve IXB	Monocytes %	♂ R		♂ N		♀ R		♀ N	
		Total	%	Total	%	Total	%	Total	%
1	0 — 6	675	66.3	125	62.5	1 543	69.2	186	74.4
2	6.1— 8	188	18.5	35	17.5	368	16.5	39	15.6
3	8.1—10	96	9.4	17	8.5	182	8.2	11	4.4
4 . . .	10.1—12	35	3.5	15	7.5	72	3.2	9	3.6
	>12	23	2.3	8	4.0	64	2.9	5	2.0

Curve IX. *Monocytes.*



In some cases in the R-material I have been able to prove pronounced deviations from normal conditions. The frequency of the changes is very high. Is one now justified in regarding these changes as really being entirely due to the effect of irradiation? Firstly, in the R-material changes of the same type as those described in the literature were manifested and these had been studied experimentally among both human beings and animals. This is positive support to the inquiry. The strongest proof, however, is that in most cases the changes are in direct connection with defects in the protective arrangements of the working quarters. The worse

Table X.

Blood *changes* arranged according to diagnosis	Total cases	%	*Injuries* of the blood arranged according to diagnosis	Total cases	%
Granulocytopenias	253	16.1	Granulocytopenias	12	0.8
Shift to the left	153	9.6		—	—
Morphological changes . . .	92	5.8		—	—
Leukopenias	60	3.8	Leukopenias	39	2.5
Anemias	74	4.7	Anemias	10	0.6
»Combined changes» . . .	190	12.6	»Combined changes» . . .	30	1.9

the arrangements have been, the greater is the frequency of the changes. It is not a 100 % correlation (leukocytosis deviates), which is the unexpected, however. The individual is obviously more or less resistent or sensitive to the irradiation, and changes which arise must be very individually accentuated. Therefore with the greatest certainty it can be said that the changes are due to irradiation. They are purely reactive and in most cases they are reversible which was observed in cases where a number of blood controls were performed.

The practically important question as to whether the changes should be apprehended as injuries or not is incapable of being answered objectively now. Under no circumstance may they be neglected. The occurrence of a change during work must be repeatedly controlled many times. Real injuries are rare in my material but these were not to be expected either. To real injuries I would only refer the following changes:

1. persistent granulocytopenia and leukopenia,
2. combined and pronounced changes and
3. grave changes (Hbl < 62 %, red bl. corp. < 3.2 milj., leukopenia $< 3{,}000$ and lymphocytosis > 60 %).

The frequency of these *injuries* comprise 6 % (see table X). The most serious injury is undoubtedly anemia. In my material anemia occurs very sparsely which is not surprising in consideration of the slight intensity of the irradiation.

This material without doubt calls attention to the possibility that with accurate blood controls of persons engaged in radiologic work the risks entailed will be pointed out. By means of a centralization of the most important blood investigations we shall get a better insight into, and a surer conception of the blood changes. The circulars compiled by the Radiofysiska Institutionen of the Karolinska Institutet is to be somewhat more detailed — even with regard to their non-blood changes. The most important measures for the prevention of irradiation injuries are principally the superintendance of the effectivity of the protection from the rays in the working quarters, and the supervision of the blood pictures. Up to the present the inspection has taken place every year but probably this

supervision must be made at shorter intervals — with respect to blood changes observed at quarters lacking in satisfactory protection. When persons engage in radiologic work for the first time care should be taken that no preformed blood changes exist.

SUMMARY

Among radiologic workers (458 men and 1,108 women) 52 % have revealed both quantitative and qualitative blood changes — leukopenia, granulocytopenia, increased »shift to the left», hypersegmentation and pathologic lymphocytes, eosinophilia and basophilia, tendency to leukocytosis, polycytemia and anemia. The changes are due to the effect of the rays and in most cases are directly connected with defects in the protective arrangements at the various working places. The blood changes are almost reactive and should then not be looked upon as serious injuries. Serious injuries are rare and have a frequency of 6 %. No very serious cases of anemia have been observed.

The present material is the greatest hitherto published investigation of this type.

ZUSAMMENFASSUNG

Unter radiologisch arbeitenden Menschen (458 Männern und 1,108 Frauen) haben 52 % sowohl quantitative als auch qualitative Blutveränderungen aufgewiesen — Leukopenie, Granulozytopenie, Linksverschiebung, Hypersegmentation und pathologische Lymphozyten, Eosinophilie und Basophilie, Neigung zu Leukozytose, Polyzytämie und Anämie. Die Veränderungen sind durch die Wirkung der Strahlen bedingt und in der Mehrzahl der Fälle direkt auf Unzulänglichkeiten der Schutzvorrichtungen an den verschiedenen Arbeitsstellen zurückzuführen. Die Blutveränderungen sind fast immer reaktiver Natur und dann nicht als ernste Schäden aufzufassen. Ernste Schäden sind selten — sie haben eine Häufigkeit von 6 %. Es wurden keine besonders ernsten Fälle von Anämie beobachtet.

Das hier vorliegende Material stellt die grösste bisher veröffentlichte Untersuchung dieser Art dar.

RÉSUMÉ

Dans un ensemble de 458 hommes et 1108 femmes travaillant avec les rayons roentgen, 52 % ont présenté des altérations sanguines tant quantitatives que qualitatives — leucopénie, granulocytopénie, augmentation de la »déviation vers la gauche», hypersegmentation et lymphocytes pathologiques, éosinophilie et basophilie, tendance à la leucocytose, polycythémie et anémie. Ces altérations sont dues à l'action des rayons, et dans la plupart des cas directement attribuables à des défauts des agencements de protection existant dans les divers laboratoires. Les modifications du sang sont presque toujours de simples réactions et ne devraient alors pas être considérées comme des lésions graves. Celles-ci sont rares, et leur fréquence est de 6 %. On n'a pas observé de cas sévères d'anémie.

Le matériel présenté ici provient de la plus grande enquête de ce genre publiée jusqu'à ce jour.

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AUS DER RÖNTGENABTEILUNG, CENTRALLASARETTET, ESKILSTUNA
(CHEF: OLOF SANDSTRÖM)

DIE RÖNTGENDOSISVERTEILUNG IM THORAX[1]

Experimentelle Untersuchung

von

Olof Sandström

Dieser Aufsatz, der eine vorläufige Mitteilung darstellt, ist ein Auszug aus dem experimentellen Teil einer grösseren Untersuchung über die direkte Herddosierung bei Teleröntgentherapie, die der Verfasser später zu veröffentlichen gedenkt. Die experimentellen Untersuchungen wurden während der Jahre 1941—1942 ausgeführt, und die Arbeit konnte u. a. infolge des Krieges und der damit verbundenen schwierigen Arbeitsverhältnisse in ihrer Gänze bisher nicht veröffentlicht werden.

Für die praktische Arbeit in der Tiefentherapie hat sich die Anwendung der kleinen Kondensator-Kammern nach SIEVERT für die Dosiskontrolle als wertvoll erwiesen, und zwar sowohl in der Oberflächentherapie wie auch in den Fällen der Tiefentherapie, in denen der Krankheitsherd von aussen her zugänglich ist. Die Vorteile dieser Kammer zeigen sich auch bei experimentellen Phantommessungen, an Leichen oder bei Tierversuchen, durch die eine genauere Kenntnis der Dosisverteilung in der bestrahlten Region erhalten werden soll. Für die theoretische Berechnung der Tiefendosis sind wir weiterhin hauptsächlich auf Phantommessungen angewiesen, die in Wasser, Paraffin, Wachs oder Reis ausgeführt werden.

PACKARD hat, im Jahre 1938, fünf verschiedene Herddosierungstabellen von HOLTHUSEN-BRAUN, PARKER und HONEYBURNE, MAYNEORD und ROBERTS, GREBE und NITZGE, QUIMBY und COPELAND gegenübergestellt und dabei gefunden, dass ein für die praktische Anwendung nennenswerter Unterschied nicht besteht. Der vorliegenden Dosierungsmethode liegen die von GREBE und NITZGE angegebenen Werte, die später teilweise von THORÆUS kontrolliert sind, zugrunde.

Alle Tiefendosismessungen sind von den Eigenschaften der Ionisationskammer und von der Homogenität des Mediums abhängig. Da der menschliche Körper ein heterogenes Medium darstellt, treten in gewissem Masse unbeherrschbare Faktoren hinzu; dies hat zur Folge, dass man eine

[1] Bei der Red. am 4. Jan. 1946 eingegangen.

grosse Genauigkeit bei der Tiefendosierung nicht verlangen kann. In der Literatur liegen verschiedene Arbeiten über Tiefendosismessungen in Körpergewebe vor, und zwar hauptsächlich in konservierten Leichen, aber auch in gewissen Gewebeschichten von frisch geschlachteten Tieren. Einen guten kritischen Sammelbericht (1934) haben QUIMBY, COPELAND und WOODES zu ihren eingehenden experimentellen Untersuchungen an in Phenol und Glycerin konservierten Menschenleichen gefügt. Die Kurve für »pelvis» entspricht der für Körpergewebe allgemeingültigen Dosisverteilung in der Richtung des Zentralstrahls, während die Kurven für Brust und Oberschenkel am meisten von der Intensitätskurve des Wassers abweichen.

Was die Dosisverteilung im Brustraum im Vergleich zu der in Wasser anbetrifft, so geben QIUMBY und Mitarbeiter ebenfalls Korrektionskurven für verschiedene Feldgrössen und Tiefen an und errechnen, dass beispielsweise bei einem Feld von 200 cm^2 und 10 cm Tiefe die Tiefendosis 23% grösser in der Lunge als in Wasser ist. Diese Untersuchungen an der Leiche und die vergleichenden Tiefenmessungen am lebenden Menschen sind ein guter Beleg für die Legitimität des Wasserphantoms als Medium für die Berechnung von Tiefendosen bei Menschen mit Ausnahme für Brustraum und die oberen Luftwege im Kopf sowie für Körperregionen mit grösserer Knochen- und Muskeldicke.

Um ein genaueres Bild über die Dosisverteilung in verschiedenen Tiefen von Lungengeweben unter so weit wie möglich normalen Bedingungen in Bezug auf den Luftgehalt zu erhalten, habe ich eine Anzahl von Messungen an Lungen von frisch geschlachteten Kälbern ausgeführt. Unmittelbar vor der Schlachtung des Kalbes wurde der intrapleurale, negative Luftdruck gemessen. Es zeigte sich, dass dieser bei 2—3 Wochen alten Kälbern gegenüber dem bei 8 Wochen alten Mastkälbern variiert. Der Mitteldruck war bei kleinen Kälbern etwa 100 mm Wasser. Bei grossen Kälbern stieg er bis 150 mm Wasserdruck. Die Experimentvorrichtung geht aus Bild 1 hervor. Mit einem Zentrifugalventilator (a), der mit einem Widerstand (b) für die Grobregulierung des Druckes versehen ist, wurde die Luft durch eine mittels einer T-Kopplung mit dem Manometer (c) verbundene Schlauchleitung zu 100—150 mm Wasserdruck angeblasen. Das mit einer Glasrörhre versehene freie Ende des Schlauchs wurde in die Trachea oder Hauptbronchie eingeführt. In der Lunge (e) ist die Lage der Sievert-Kammer (—) schematisch angegeben. Das Experiment wurde 3—24 Stunden nachdem die Kalblungen herausgenommen waren ausgeführt. Um normale Verhältnisse noch weiter zu rekonstruieren, wurde bei der Schlachtung die halbe Brustkorbswand mit Muskeln mit herausgenommen. Da es sich als schwierig erwies, eine Bestrahlung von einem Rückenfeld durch die dicke Rückenmuskulatur zu veranschaulichen, wurden sämtliche Bestrahlungen auf ein Seitenfeld gemacht. Die variie-

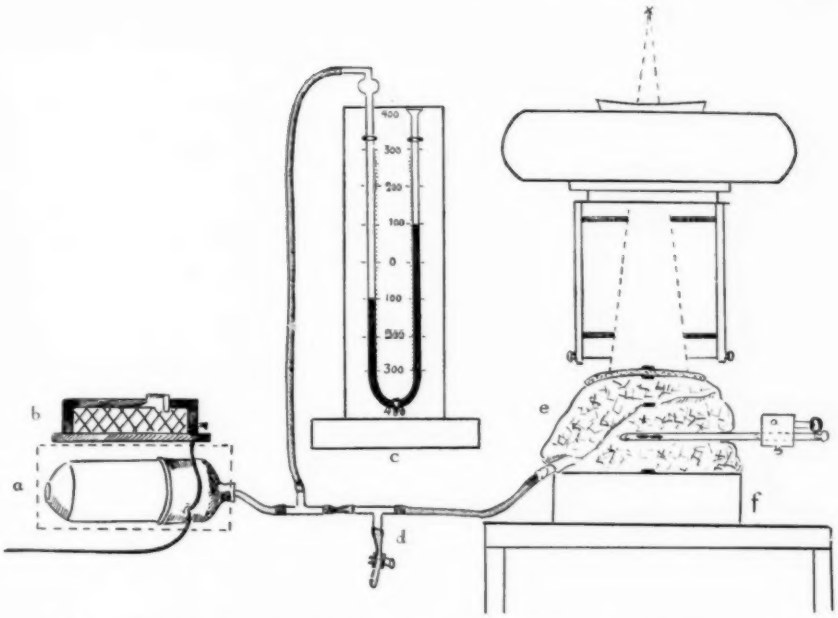

Bild 1. Die Experimentvorrichtung bei den beschriebenen Dosismessungen an Kalblungen.

rende Muskeldicke wurde bei einigen Experimenten durch eine zusätzliche Schicht von einer 2 cm dicken Muskelschicht auf der Thoraxwand zum Ausdruck gebracht. Die experimentellen Bedingungen sind, soweit möglich, naturgetreu gestaltet worden, jedoch mit einer Ausnahme, nämlich der normalen Blutfüllung. Bei der Intensitätsmessung diente als Unterlage für die Lungen eine 5 cm dicke Holzplatte.

Bei den Tiefenmessungen wurde SIEVERTS kleine Kondensatorkammer angewandt. Da diese Kammern feuchtigkeitsempfindlich sind und die Tiefenmessungen intrapulmonal auszuführen waren, musste eine passende Experimentvorrichtung hierfür gefunden werden. Da ausserdem die genaue Bestimmung der Herdtiefe bei jeder Tiefenbehandlung einer der wichtigsten Faktoren ist, liess ich ein Instrument ausführen, das diesen beiden Forderungen Rechnung trug, indem es die Kammern trocken hält und eine genaue Bestimmung der »Herdtiefe» ermöglicht. Bei der Wahl des Materials für den Kammerhalter kam es darauf an, dass dessen Absorptionsvermögen dem des Körpergewebes so nahe wie möglich kam. Nach Prüfung und Absorptionsmessungen an verschiedenem Material

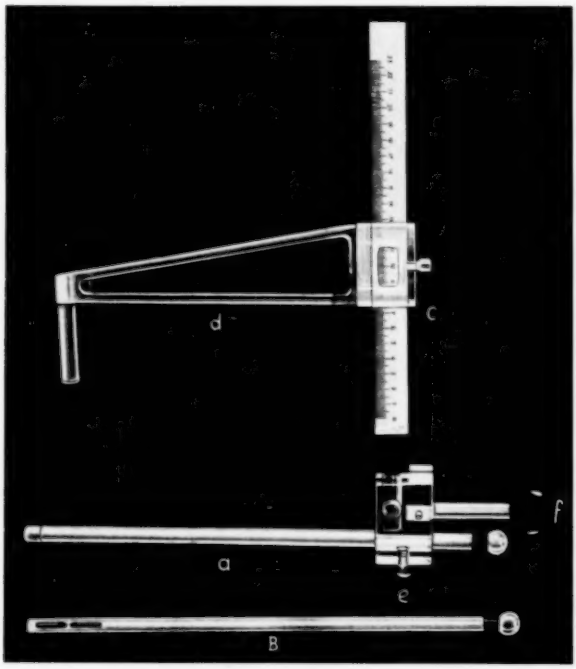

Bild 2. Hilfsgerät für Dosismessungen mit SIEVERT-Kammer im Körper.

entschloss ich mich für Plexiglas. Das spezifische Gewicht von Plexiglas ist 1.10. Durch seine übrigen Eigenschaften sowie seinen Härtegrad und seine Elastizität ist es für feinmechanische Arbeiten gut geeignet. Aus mehreren Erwägungen erschien es daher vorteilhaft, dieses Material für das ganze Instrument anzuwenden.

Das Instrument (s. Bild 2) besteht aus einer im freien Ende geschlossenen Röhre (A), die in Körpergewebe oder Hohlräume hineingeschoben wird, und einem in der Röhre verschiebbaren Halter (B) mit einer Aushöhlung an der Spitze für zwei Kammern. Das Aussehen des Messinstruments im übrigen geht aus der Abbildung hervor.

Aus dem Diagramm (Bild 3) geht das Resultat der experimentellen Untersuchung über die Verteilung der Dosis in der Tiefe bei Lungengewebe vom Kalb im Vergleich zum Wasserphantom hervor. Die experimentellen Betriebsbedingungen sind unter dem Diagramm angegeben. Die Kurven geben die Dosisverteilung in Prozenten der Oberflächendosis

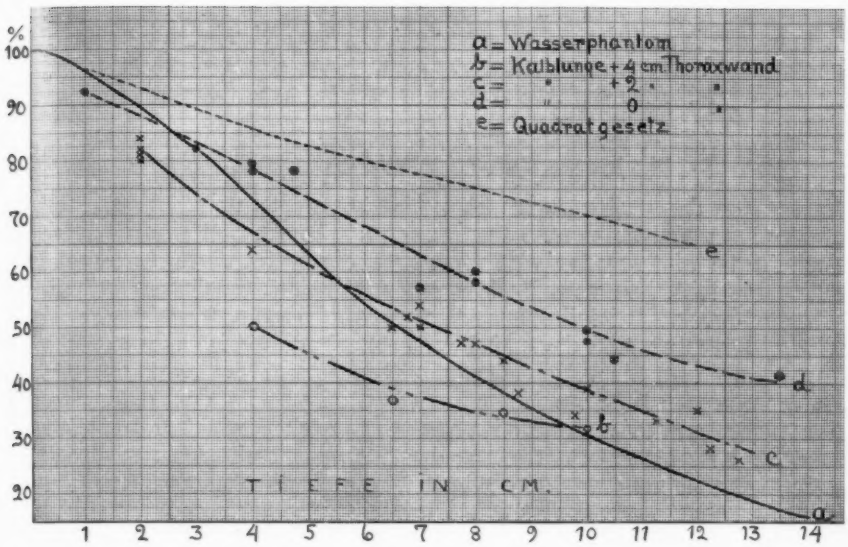

Bild 3. Diagramm über die Röntgendosisverteilung in der Kalblunge in Vergleich zu derjenigen im Wasserphantom. Röhrenspannung 169 kV konstante Gleichspannung. Filter: 0.5 mm Cu + 1 mm Al, HWS: 0.95, Feldgrösse 100 cm². Focusabstand: 60 cm.

bei verschiedener Tiefe an. Die Vergleichskurve für Wasserphantom stammt aus einer von BENNER und LINDBLOM mit SIEVERTS kleinen Kondensatorkammern am Radiumhemmet in Stockholm ausgeführten Untersuchung. Auf Bild 3 sind teils eine Tiefendosiskurve ausschliesslich für Lungengewebe beim Kalb, teils 2 Kurven für Lungengewebe mit darüberliegender Brustkorbswand angegeben, deren Dicke für die beiden Kurven 2 bzw. 4 cm ist. Dir Kurven für Lungengewebe sind als Mittelwert der Messungen angegeben, die aus der Punktreihe auf dem Diagramm hervorgehen.

Die experimentelle Untersuchung zeigt, dass die Kurven von Wasser und Lungengewebe beim Kalb plus 2 cm Thoraxwand einander bei einer Tiefe von 5—6 cm schneiden. Ein Vergleich dieser Kurve mit den beiden übrigen für Lungengewebe zeigt, dass die *Dicke der Brustwand von entscheidender Bedeutung für die Lage der Tiefendosiskurve des Lungengewebes zu derjenigen des Wasserphantomes ist* und dass die Brustwand je nach ihrer Dicke der wegen des Luftgehaltes der Lungen erwarteten Erhöhung der Tiefendosis entgegenwirkt.

Die experimentellen Untersuchungen an sowohl der konservierten

Menschenleiche wie an frisch geschlachteten Kälbern können als Richtschnur für die praktische Dosierung gut dienen. Beim lebenden Menschen kommen jedoch gewisse Faktoren hinzu, die in Betracht zu ziehen sind: In erster Reihe ist die normale, gleichmässig verteilte Luftfüllung der Lungen zu berücksichtigen.

Bei QUIMBY's Untersuchung hat man einer Luftfüllung Rechnung zu tragen, die teils wegen der postmortalen Schrumpfung des Thorax, teils wegen der postmortalen Stasveränderungen in der Lungen selbst, nicht als normal bezeichnet werden kann. Die Lungen sind blutgefüllt, doch ist die Blutmasse mit Rücksicht auf die postmortale Stase ungleichmässig verteilt. Die vom Verfasser benutzte Untersuchungsvorrichtung gibt die normale Luftfüllung der Lungengewebe auf naturgetreuere Weise wieder. Hingegen sind diese Experimentlungen anämisch. Eine der Voraussetzungen für die Vergleichsmöglichkeit verschiedener experimenteller Untersuchungen über die Tiefendosen in der Brust ist, dass die Dicke der Brustkorbswand die gleiche ist, da diese nach Ansicht des Verfassers wesentlich ist für die Beurteilung der Lage der Tiefendosiskurve. QUIMBY's Untersuchung an konservierten Menschenleichen und die Untersuchung des Verfassers an Kalblungen plus 2 cm Thoraxwand zeigen in dieser Hinsicht eine gute Übereinstimmung, da die Schnittpunkte der Kurven für Wasser und für Lungengewebe in beiden Fällen bei 5—6 cm Tiefe liegen.

Man hat im Brustkorb einerseits mit dem lufthaltigen Lungengewebe mit verminderter Absorption und verminderter Rückstreuung im Vergleich zum Wasserphantom zu rechnen, anderseits mit dem Muskel- und Knochengewebe mit erhöhter Strahlenabsorption und hinsichtlich des Knochengewebes mit einer verminderten Rückstreuung im Vergleich zu Wasser. Die Lage der Tiefendosiskurve hängt also in erster Reihe von der Schichtdicke der einen oder anderen Gewebe innerhalb des Thorax ab. Bei der Behandlung intrathorakaler Prozesse kommt jedoch neben der Schichtdicke der normalen Gewebe ein weiterer die Tiefendosiskurve beeinflussender Faktor hinzu, nämlich die Lage des Tumors und seine Ausbreitung im Thorax. Eine allgemein gültige Korrektur für die Wasserkurve bei intrathorakalen Prozessen ist somit nicht feststellbar. Diese ist vielmehr abhängig von den Verhältnissen des Einzelfalles, nämlich sowohl der Grösse des Thorax und der Dicke der Brustkorbswand auf der einen Seite wie der Lage des Tumors und seiner Ausdehnung im Verhältnis zu den Bestrahlungsfeldern auf der anderen. Jedoch kann den Kurven des Verfassers ein Wert als Richtschnur für die theoretische Berechnung der Herddosis beigemessen werden.

ZUSAMMENFASSUNG

Der Verfasser hat Intensitätsbestimmungen mit den kleinen Kondensatorkammern nach SIEVERT in verschiedenen Tiefen an Lungen von frischgeschlachtetern Kälbern bei wechselnder Dicke der Brustkorbwand ausgeführt. Die Experimentvorrichtung wird beschrieben, und die Resultate werden in einem Diagramm zusammengestellt. Die Kurven geben die Röntgendosisverteilung in Hundertsteln der Oberflächendosis bei verschiedener Tiefe an. Verf. vergleicht siene Ergebnisse mit denen von QUIMBY u. a. bei Intensitätsmessungen an konservierten Menschenleichen.

SUMMARY

The author has carried out experiments for the determination of intensity with SIEVERT's small condensor chamber at different depths in the lungs of newly slaughtered calves with varying thicknesses of the thoracic wall. The experimental appliance is described and the results have been set up in a diagram. The curves in this give the apportionment of the roentgen doses at different depths in hundredth of the surface dose. The author compares his results with those obtained by QUIMBY and others in measuring the intensity in preserved human corpses.

RÉSUMÉ

L'auteur a fait de la dosimétrie avec les microchambres ionométriques de SIEVERT à différentes profondeurs des poumons de veaux qui venaient d'être abattus et dont la paroi thoracique avait des épaisseurs variables. Il décrit l'agencement des expériences et en récapitule les résultats sur un diagramme. Les courbes indiquent la distribution des doses de rayons roentgen à des profondeurs différentes en centièmes de la dose cutanée. Il compare ses résultats à ceux de QUIMBY et d'autres auteurs qui ont mesuré l'intensité sur des cadavres humains conservés.

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(HEAD: PROF. H. SLÄTIS)

ON THE γ-RADIATION FROM POLONIUM[1]

by

Kai Siegbahn and *Hilding Slätis*

1. Earlier Investigations

In connection with the study of the secondary radiation emitted when a number of light elements were subjected in turn to the α-radiation emitted by a strong Po sample, BOTHE and BECKER (2) found that Po also emitted a (hard) γ-radiation. The intensity of this, however, was low, about one γ-quantum being emitted for 10^5 α-particles. The Po sample had been deposited upon a thin silver foil, so that it might be suspected that the radiation was emitted secondarily from Ag. Special experiments showed, however, that α-radiation could not produce any appreciable secondary radiation from silver. The γ-radiation of Po was interpreted as resulting from the fact that one of 10^5 α-particles was emitted with lower energy than the rest, leaving the nucleus in an excited state, from which it returned to the ground state with emission of a γ-quantum.

BOTHE (3) subsequently investigated the secondary β-radiation (K-electrons from ^{206}Pb) from the sample, caused as he thought, by the γ-radiation, by means of a β-spectrograph of high light intensity (semi-circular method). The source of radiation here was Po, deposited on both sides of a silver foil 0.1 mm thick. The silver foil rested on a substratum of brass. The activity was c. 30 millicuries. The effective space-angle of the spectrometer was $4\pi/40$, the theoretically calculated resolving power amounting to 7 %.

The results obtained by BOTHE have been reproduced in Fig. 3 (curve *b*). The β-spectrum shows three certain and two uncertain maxima, which were thought to be due to an internal-conversion effect in the sample ^{206}Pb). In the calculation of the energies of the corresponding γ-lines, therefore, the ionization work for the K-electrons in the Pb atom, 88 keV,

[1] Submitted for publication, February 15, 1946.

was added to the energies corresponding to the maxima 114, (267), (345), 710 and 980 keV. The five maxima were hence thought to be due to γ-lines with the energies 202, (355), (433), 798 and 1068 keV. (The values corresponding to uncertain maxima have been placed in brackets.)

In a later investigation BOTHE (4) studied the secondary β-spectra due to the γ-radiation from some lighter nuclei which were excited by α-particles from Po. Here the Po, as the only γ-radiating substance, was enclosed in a lead capsule with walls 0.6 to 1 mm thick. In this manner a Compton and photo spectrum was obtained which is reproduced in Fig. 3, curve *c*. According to the figure, the maximum energy of the Compton electrons lies at $H\varrho = 4700$, corresponding to a γ-radiation energy $E \approx 1.2$ meV (20). It can thus be established that according to BOTHE's results, γ-energies greater than 1.2 meV should not occur in Po. Regarding other results, it may be mentioned that in the study of Be_4^9, which is converted by a (α, n) process to C_6^{12}, three γ-radiation energies were observed, namely at 2.7, 4.2 and 6.7 MeV.

The previously mentioned interpretation of the γ-radiation from Po requires a fine structure in the α-particles. ROSENBLUM (15), and RUTHERFORD and co-workers (16) sought for this in vain. By the use of a large, magnetic α-spectrograph, CHANG (5) recently succeeded in finding quite a complicated fine structure, consisting of 12 different ranges apart from the maximum. The values obtained by this author are given in Table 2 (§ 7). CHANG describes the ratio found by BOTHE, 7 γ-quanta to 10^6 α-particles, as uncertain. According to CHANG's table, this ratio would be considerably greater, approx. 1 : 1000.

2. The Position of Polonium in the Radium Family

Po_{84} or RaF, the last active nucleus in the radium family, is α-radiating with a particle energy of 5.403 MeV and a half-life period of 140^d (13). Po is formed from RaD according to the following scheme:

$$RaD_{82}^{210} \xrightarrow{22^y} RaE_{83}^{210} \xrightarrow{5^d} RaF_{84}^{210} = Po \xrightarrow{140^d} RaG_{82}^{206}$$

β (0.0255 MeV) β (1.17 MeV) γ α (5.403 MeV)

These nuclei are isotopes of Pb, Bi, Po and Pb respectively.

3. The Isolation of Polonium

RaD is gradually deposited on the insides of RaEm tubes and can be isolated by crushing old emanation tubes and boiling them in nitric acid,

the RaD passing into solution. Po can be deposited on metallic silver from a solution of RaD in hydrochloric acid (6). According to KOHLRAUSCH (23), Po can be won from radio-lead acetate free from RaD and RaE by electrolytic deposition on a Pt cathode at low current density. Po can also be separated in the form of peroxide by electrolytic deposition on Pt electrodes. Strong samples are obtained by repeated electrolysis and distillation into a small receiver of platinum or palladium in a current of hydrogen (14). The cathodic deposition, however, does not yield pure products (7).

4. The Po Sample

We had at our disposal a solution of RaD obtained from old RaEm tubes in the manner outlined above. Apart from RaD and its associated materials, the solution contained the acid radicals NO_3, CH_3COO and Cl. The γ-radiation emitted by the solution (volume approx. 16 cc) was first investigated by absorption measurements (see below). An attempt to precipitate Po from solution in hydrochloric acid was unsuccessful, apparently because of the impurity of the material. The solution was therefore evaporated down, and the residue, a soft mass of about 0.2 cc volume, was enclosed in a copper cylinder, the lid of which was hermetically sealed with wax. The external diameter of the cylinder was 8 mm and the length 10 mm. The wall-thickness amounted to 1.6 mm, so that the β-radiation from RaE (and naturally also the α-radiation) was certainly screened off. The cylinder was covered with a thin lead foil and the energies of the photo and Compton electrons produced in this were studied in a magnetic lens-spectrograph of high light intensity (18) (§ 6).

5. Absorption Measurements

In the absorption measurements the intensity of the γ-radiation was determined with a brass Geiger Müller tube, a Neher-Harper circuit, a scale of eight and a mechanical counter. The sample and the Geiger-Müller tube were separated by a lead armour 15 cm thick, through which a channel of 2×4 cm^2 cross section permitted the radiation from the sample to reach the Geiger-Müller tube. The latter was 20 cm from the sample.

Fig. 1 shows the intensity of the radiation as a function of the thickness of the lead absorbers placed in the radiation path. The magnitude of the systematic errors has been marked with double arrows. We observe a soft radiation, probably complex in character, since a definite half-value thickness cannot be derived from the absorption curve. The value of this is at all events greater than 0.016 mm Pb. Hence the wave-length is less

than 0.1 Å (21) and the energy of the radiation greater than 0.125 MeV (22). We find, moreover, a harder component, the half-value thickness for which is 15.4 mm Pb. According to GENTNER's correlation (9) this corresponds to an energy of $\approx$ 2.6 MeV.

Fig. 2 shows a more accurate registration (one-hour measurement intervals for the lower intensities) made after the sample had been evaporated down and enclosed in the copper cylinder earlier described. Apart from the hard radiation, for the energy of which the value 2.6 MeV was also obtained here, a component of medium hardness is also observed, corresponding to a half-value thickness of 4.2 mm Pb and hence to an energy of $\approx$ 0.5 MeV. The previously observed soft radiation is also apparent.

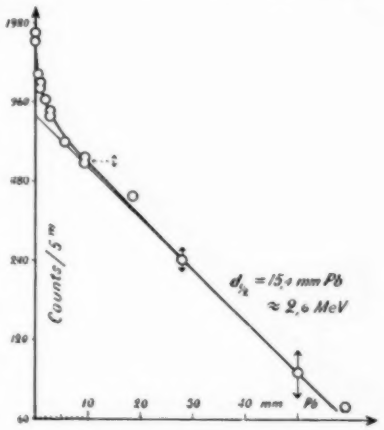

Fig. 1. The intensity of the γ-radiation as a function of the thickness of the lead absorbers.

The activity of the sample, measured for the harder components, was $\approx$ 3 microcuries Ra γ-equivalence.

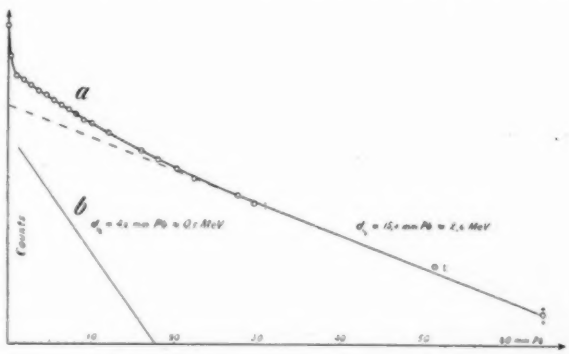

Fig. 2.
(a) The intensity of the γ-radiation as a function of the thickness of the lead absorbers.
(b) The total intensity of the radiation diminished by the hardest component.

6. The Photo and Compton Electrons

The emission of Compton and photo electrons in the lead sheath caused by the γ-radiation from Po, was investigated in the magnetic lens-spectrograph. The shutter system was such that 2 % of the total β-radiation was

recorded. The resolving power of the instrument was in this case $\frac{\Delta H\varrho}{H\varrho}=5\%$. Fig. 3a shows the electron spectrum obtained here, *i. e.* the number of electrons registered as a function of the current strength in the coil or,

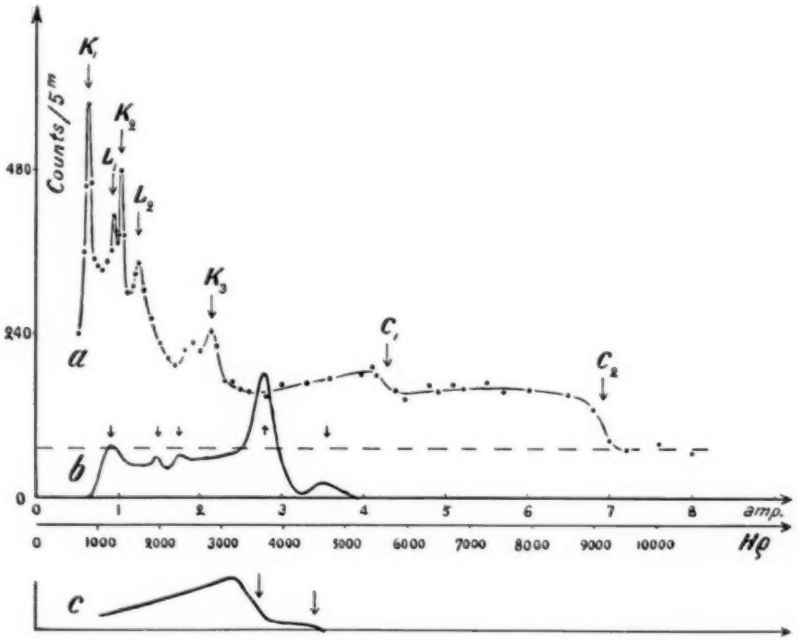

Fig. 3. (a) The intensities of the photo and Compton electrons as functions of their momenta.
(b) The β-spectrum of Po deposited on thin silver foil (after Bothe).
(c) The β-spectrum of Po enclosed in a lead capsule 0.6—1 mm thick (after Bothe).

consequently, as a function of $H\varrho$. Five photo lines are seen, denoted in the figure by K_1, L_1, K_2, L_2 and K_3, as well as at least two Compton lines, denoted as C_1 and C_2. The energies E_β of the photo lines have been calculated in MeV from the formula (19)

$$E_\beta = 0.51089\left\{\sqrt{1+\frac{(H\varrho)^2}{2.9052\cdot 10^6}}-1\right\}$$

When the works of ionization of the K- and L-electrons in lead, 0.088 and 0.016 MeV respectively, are added to the values thus obtained, the energies of the corresponding γ-lines result.

The γ-radiation energies corresponding to the Compton lines were found from the formula (20)

$$E = \frac{0.51089}{\sqrt{1 + \frac{(H\varrho)^2}{2.9052 \cdot 10^6}} + 1} - 1$$

where $H\varrho$ denotes the reading for the Compton edge in the diagram.

Table 1 shows the energies of the components of the γ-radiation thus calculated (fifth column). The first column indicates the line or Compton edge in question.

Table 1.

Line	$H\varrho$	E_β	E_γ	E_γ (mean)
K_1	820	0.056 MeV	0.144 MeV	0.14 MeV
L_1	1 240	0.120 »	0.136 »	
K_2	1 380	0.145 »	0.233 »	0.23 »
L_2	1 687	0.210 »	0.226 »	
K_3	2 800	0.470 »	0.558 »	0.56 »
C_1	5 540	1.225 »	1.450 »	1.45 »
C_2	9 150	2.270 »	2.510 »	2.51 »

The results display good agreement with the absorption measurements. We thus have two softer radiations with the energies 0.14 and 0.23 MeV, one with 0.56 MeV, corresponding well with the approximate value 0.5 MeV found in the absorption measurements, and a hard radiation with the energy 2.51 MeV. The corresponding value for the latter in the absorption measurements was 2.6 MeV. The radiation at 1.45 MeV, however, seems to have been too weak to be detected in the absorption measurements. The path of the curve *a* between the Compton edges C_1 and C_2 does not exclude the possibility of one or more weaker γ-radiation components of energies between 1.45 and 2.51 MeV, although their intensities would be so low that they could not be resolved in the case of the present, extremely weak sample. It is also possible that a weak K-line occurs immediately to the left of K_3 for $H\varrho \approx 2500$. This would correspond to a γ-radiation energy of 0.47 MeV.

7. Discussion

Figs. 3*b* and 3*c* show the results of BOTHE (l. c.), *b* when Po was deposited on a thin Ag foil, and *c* when the sample was enclosed in a small Pb capsule with walls 1 mm thick. It will be seen that the forms of the two

recordings are somewhat different. This is not remarkable in view of the essentially different origins of the radiation in the two cases. It should, however, be very difficult to bring the two recordings into one another with what concerns the energy of, for example, the strongest γ-component. In this connection it is very surprising that this component is completely lacking in our recording.

BOTHE interpreted his lines as due to an internal-conversion effect in the sample itself, and therefore inserted the ionization work for the K-electrons in the Pb atom in his calculation of the energies of the γ-lines. Despite the relatively moderate atomic number of Ag, it seems to us not quite impossible to attribute the lines to a photo effect in Ag, since the reverse side of the silver foil also bore Po. The first line will then correspond to a γ-radiation energy of $0.114 + 0.026 = 0.140$ MeV, agreeing with the value for the softer γ-component which we found from K_1 and L_1.

CHANG (l. c.) found the energy groups reproduced in Table 2 for the α-radiation from Po (second column). The third column gives the energy levels that are consequently possible for the residual nucleus Pb^{206}. We see that three energy values, namely 0.238, 0.554 and 1.413 MeV, correspond closely with three of our γ-components, *i. e.* 0.23, 0.56 and 1.54 MeV. CHANG's value of 0.465 agrees with our uncertain γ-radiation at 0.47 MeV. In addition many transitions can be found between CHANG's energy levels corresponding to energy changes close to those found by us. This fact is, however, of minor significance, since 78 transitions are possible and must always include values of the desired magnitude.

Table 2.

Energies of groups of alpha-particles according to Chang

Group	Group Energy in MeV	$E_n = \alpha_0 - \alpha_n$ (MeV)	Relative Intensity
α_0	5.303	0	16^6
α_1	5.113 ± 0.005	0.190	(250)
α_2	5.065 ± 0.005	0.238	(250)
α_3	4.901 ± 0.005	0.402	150
α_4	4.838 ± 0.005	0.465	110
α_5	4.749 ± 0.005	0.554	130
α_6	4.640 ± 0.005	0.663	104
α_7	4.449 ± 0.005	0.854	116
α_8	4.303 ± 0.005	1.000	70
α_9	4.111 ± 0.005	1.192	75
α_{10}	4.016 ± 0.005	1.287	50
α_{11}	3.890 ± 0.005	1.413	40
α_{12}	3.685 ± 0.005	1.618	40

It is of especial interest that, according to CHANG's investigations regarding the α-spectrum, the hardest γ-radiation, the energy of which is 2.51 MeV and which also appeared in the two absorption measurements (§ 5), has no corresponding low-energy α-radiation. It is therefore probable that this γ-radiation is emitted from some foreign atomic nucleus.

In intimate contact with the α-radiating polonium are the following elements, which must be reckoned with (see above): C, N, O, Cl and Cu. The latter can immediately be excluded, since the hard γ-radiation was already emitted from the sample in aqueous solution. Of possible nuclear reactions with the remaining elements, we must first consider (α, n) and (α, p) reactions. In view of the low magnitude of the Gamov factor for Cl at the α-energy here concerned ($E_\alpha = 5.403$ MeV), this element may presumably be excluded. (G becomes equal to unity only at ~ 9 MeV.) The following table shows the remaining possible reactions. The reaction heat has been calculated for each reaction from the known mass defects.

Occurrence of isotope in %	(α, n) reaction	Δm TME	Q MeV	(α, p) reaction	Δm TME	Q MeV
98.9	C_6^{12} (α, n) O_8^{15}	− 9.00	− 8.41	C_6^{12} (α, p) N_7^{15}	− 5.26	− 4.90
99.62	N_7^{14} (α, n) F_9^{17}	− 5.13	− 4.79	N_7^{14} (α, p) O_8^{17}	− 1.24	− 1.16
99.76	O_8^{16} (α, n) Ne_{10}^{19}	−13.1	−12.2	O_8^{16} (α, p) F_9^{19}	− 8.81	− 8.23

It follows from this table that all reactions are endothermic. The reactions that might conceivably be obtained with C_6^{13}, N_7^{15}, O_8^{17} and O_8^{18} have not here been considered, in view of the small amounts in which these isotopes occur.

A part of the energy of an α-particle is transferred by the impact to the compound nucleus as energy of translation. The energy available for excitation is then

$$E_{max} = \frac{E_\alpha \cdot m_{nucleus}}{m_{nucleus} + m_\alpha} + Q$$

For C_6^{12} the first term here amounts to 4.05 MeV, for N_7^{14} to 4.20 MeV and for O_8^{16} to 4.33 MeV. In view of the observed γ-energy of 2.5 MeV, it is obvious that only N_7^{14} (α, p) O_8^{17} remains as a possible reaction. This has been quite thoroughly studied earlier. By the bombardment of N with α-particles from RaC, E. FISCHER-COLBRIE (8) demonstrated the occurrence of two distinct proton groups. The energy difference between these amounted to 1.4 MeV. A γ-radiation of this energy was also shown by E. KARA-MICHAILOVA (11) and by P. SAVEL (17). It has not been possible to show any excited state in O_8^{17} at 2.5 MeV by means of the reaction Ne_{10}^{20} (n, α) O_8^{17} (10). Among other explanations of the occurrence of the hard

γ-component may be mentioned the possibility of the capture of α-particles without the emission of heavy particles. Such a process has not as yet been observed. The condition for being able to detect such a nuclear process, according to the arguments of H. A. BETHE and G. PLACZEK (1), is fulfilled in this case for C^{12} and O^{16}, since these nuclei cannot be transformed by α-particles in any other manner.

As a final possibility there remains a type of reaction hitherto observed only in one or two individual cases, namely an inelastic dispersion of α-particles, the struck nucleus being left in an excited state. The ground state is attained by emission of one or more γ-lines. BOTHE (4) has shown that in the process Be^{9}_{4} (α, n) C^{12}_{6} three γ-lines are emitted, namely at 2.7, 4.2 and 6.7 MeV. MAIER-LEIBNITZ (See (4)), by means of coincidence experiments, has shown that the γ-radiation chiefly takes place by the emission of two γ-lines in cascade. Consequently, the following two possibilities for the term scheme of C^{12} may be suggested (Fig. 4). Which of (a) and (b) is the correct scheme cannot be decided on the basis of previous experiments. Our γ-energy of 2.5 MeV corresponds well within the limits of the methods with the γ line at 2.7 MeV. If it be assumed that this line is due to a (α, $\alpha\gamma$) process in C^{12}, it is clear that (a) must be the correct term scheme.

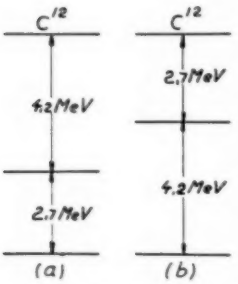

Fig. 4. Possible term schemes for C^{12}, after BOTHE.

It deserves to be pointed out that BOTHE found such an (α, $\alpha\gamma$) process in Li^{7}, where $\alpha\gamma$ radiation of max. 0.6 MeV was emitted. The probability of an inelastic spreading of α particles, however, decreases very rapidly with increased excitation energy in the excited nucleus, according to the theory of L. LANDAU (12). This renders the effective cross section for this process rather small in the case of C^{12}. Nevertheless, in view of the difficulty of explaining the hard γ line in any other manner, together with the good agreement with BOTHE's values for the excitation levels in C^{12}, the possible occurrence, despite all evidence to the contrary, of such an inelastic dispersion of α particles should be taken into consideration. When pure Po samples become available it should be possible to make more definite statements in this matter. The question must be left open for the present.

We have the pleasant duty of expressing our thanks to Professor J. C. JACOBSEN, who was kind enough to lend us the sample of RaD employed in this investigation. We wish at the same time to thank Dr. N. SVARTHOLM for valuable discussions regarding the theoretical problems connected with the work.

8. Main Results

(1) The γ-radiation emitted by Po from a RaD sample was investigated by measurements of the absorption in lead. A soft γ-radiation was detected (energy higher than 0.125 MeV) together with radiations of the energies 0.5 and 2.6 MeV.

(2) By means of a magnetic lens-spectrograph of high light intensity, an energy spectrum was recorded of the electrons released by the γ-radiation through the photo and Compton effects in a sheath of copper, covered with lead foil, surrounding the sample. γ-radiations of the energies 0.14, 0.23, 0.56, 1.45 and 2.51 MeV were detected here, while an uncertain component could be discerned at 0.47 MeV.

(3) A comparison was made of these results with the conceivable transitions between the energy levels in the residual nucleus Pb^{206}, determined by CHANG from the α-radiation of polonium. The γ-components found by us with the energies 0.23, (0.47), 0.56 and 1.56 MeV were represented by direct transitions to the ground state from the levels 0.238, 0.465, 0.554 and 1.413 MeV respectively found by CHANG. Our softest γ-component, 0.14 MeV, did not agree satisfactorily with CHANG's lowest level at 0.19 MeV.

(4) The hardest γ-radiation, with an energy 2.51 MeV, is not reconcilable with CHANG's energy levels. In the C_6^{12} nucleus resulting from a (α, n) process in Be_4^9, BOTHE found energy levels at 2.7, 4.2, and 6.7 MeV. Our RaD sample contained lead acetate and hence C^{12} nuclei. It is therefore possible that these nuclei were excited by inelastic impacts of the α-rays from Po to the lowest level 2.7 MeV and, on reversion to the ground state, emitted a γ-radiation of the said energy. This suggestion is in concord, within the limits of error, with the value of 2.51 MeV found by us, though theoretical considerations show a small cross section for this process.

SUMMARY

The very faint γ-radiation accompanying the α-disintegration of Po has been studied by means of a β-spectrograph of high light intensity. The energy distributions of the secondary electrons emitted from a copper and lead radiator were investigated. Some of the γ-rays are in concordance with the α-spectrum. The occurrence of a high-energy γ-ray is discussed.

ZUSAMMENFASSUNG

Die sehr schwache γ-Strahlung, die den α-Zerfall des Poloniums begleitet, ist in einem β-Spektrographen hoher Lichintensität untersucht worden. Die Energieverteilung der Sekundärelektronen aus Kupfer und Blei wurde gemessen. Einige γ-Energien sind in Übereinstimmung mit dem α-Spektrum. Das Auftreten von γ-Quanten hoher Energie wird diskutiert.

RÉSUMÉ

La très faible radiation γ accompagnant la α-désintégration de Po a été étudiée aux moyens d'un spectrographe à rayons β à grand facteur de transmission. On a recherché la distribution d'énergie des électrons secondaires produite par un radiateur de cuivre et de plomb. Quelques uns des rayons γ sont en concordance avec le spectre des rayons α. On a discuté la présence d'un rayon γ de haute énergie.

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FROM THE RADIOPHYSICAL INSTITUTE OF KING GUSTAF V'S JUBILEE CLINIC, STOCKHOLM
(CHIEF: PROF. R. SIEVERT)

A TRI-ELECTRODE STANDARD AIR-IONISATION CHAMBER FOR ROENTGEN RAY MEASUREMENTS IN *r*-UNITS[1]

by

R. Thoræus

In a previous paper (*Acta Radiol.* Suppl. XV, 1932) the author has described in detail the standard air-ionisation chamber used in this Laboratory for accurate measurements of roentgen rays in *r*-units and for calibrations of secondary standards and commercial dose-meters. A preliminary, rather generous estimate of the total margin of error of this primary standard gave ± 1.5 per cent in measuring the roentgen ray intensity in *r*/min. Further investigations have clearly shown, however, that the margin can be reduced to about ± 1 per cent if every precaution and the best care are taken. This standard chamber has been in frequent use for about fourteen years, and has proved extremely reliable and convenient for all kinds of experimental work. Measurements of half-value layers are rather tedious, however, since at least four different absorption readings must be taken to determine each half-valuelayer satisfactorily. To eliminate this the standard chamber has been provided with an additional device for insertion into the cylindrical standard chamber as a substitute for the ordinary measuring electrode. By this reconstruction of the standard chamber other advantages will also be gained, particularly in the calibration of secondary standards.

This reconstruction was planned and designed in principle already in 1938—1939. For various reasons, however, its definite completion and trial were delayed until 1945. The purpose of this article is to describe the reconstructed standard chamber and its particular features, and in addition to demonstrate some measuring results obtained a) in comparing the old standard chamber with its amended edition, and b) in particular ranges of application characteristic of the latter.

[1] Submitted for publication, Jan. 28, 1946.

Description of the new measuring device

The new measuring device is illustrated in figs. 1 and 2. It consists of one central electrode, containing two plane measuring electrodes and two side electrodes, each 121 mm from the central electrode. The side and central electrodes are rigidly fastened to two bakelite plates, one at each end of the electrodes, thus forming a measuring unit to be inserted into the old cylinder of laminated paper, which is lined with a thin layer of aluminium. This layer is earthed, thus providing an electrostatic shield

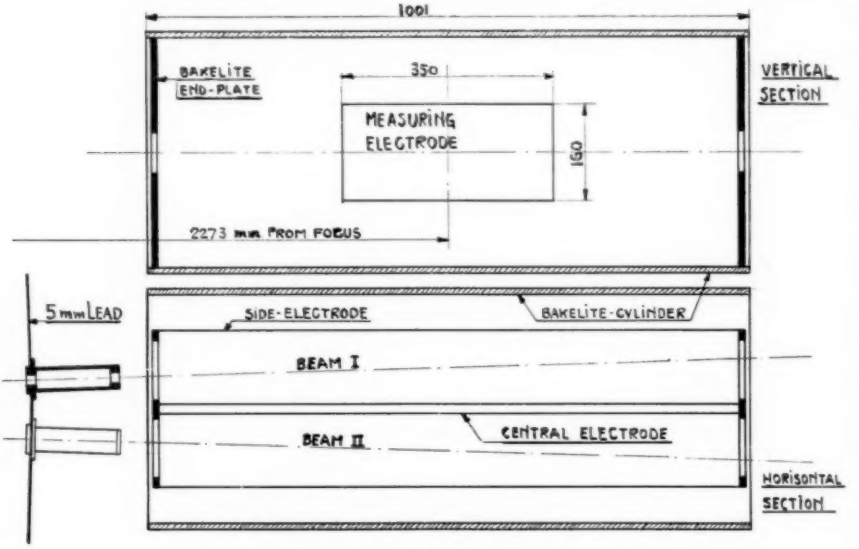

Fig. 1.

all round the measuring unit. The bakelite end plates are provided with wide openings, 70 × 95 mm, for the passage of the beams.

The central electrode consists of two aluminium plates, 2 mm thick and 13 mm apart, between which a 3 mm lead plate is built in as protection from radiation. The central portion of each aluminium plate is removed, thus leaving openings into which the measuring electrodes of 1 × 350 × 160 mm aluminium plate are inserted and fastened by amber insulators, the surrounding parts of the 2 mm aluminium plates being used as guard electrodes. The measuring electrodes are independent of and insulated from each other, and may be connected to earth or to the measuring electrometer system as desired. The other parts of the central electrode are connected to earth.

The side electrodes are also independent of and insulated from each other and may be connected either to earth or to the plus or minus terminal of a 3.000 volt battery. By connecting the centre of the battery to earth a difference in potential of plus or minus 1500 volt may be

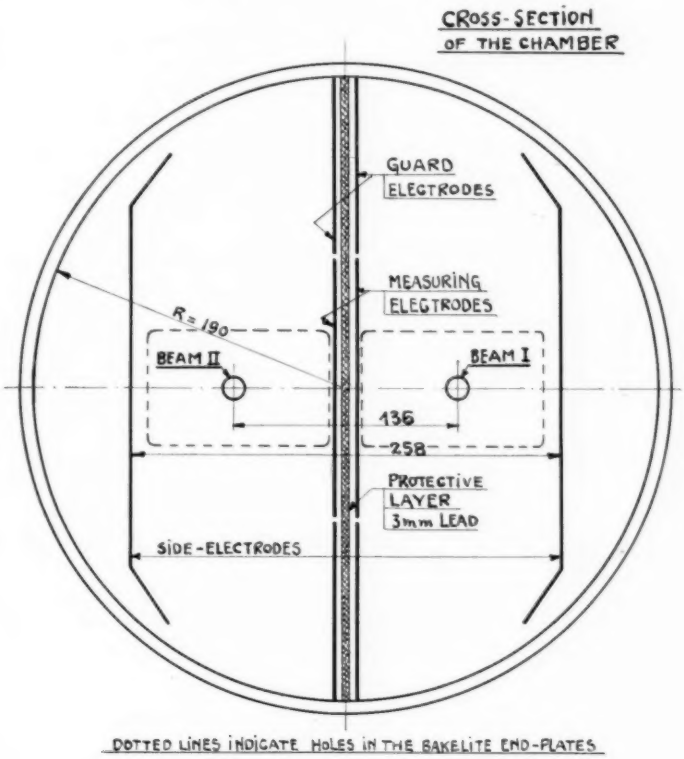

Fig. 2.

obtained between the side electrodes and the central electrode to assure saturation current when measuring the ionisation produced by the beams.

At a focal distance of 1,599 mm a protective shield of 5 mm lead plate is arranged, into holes of which diaphragms of different apertures may be inserted to determine the cross section of the beams. A 140 mm long lead tube is arranged behind each diaphragm to prevent secondary radiation from one diaphragm influencing the ionisation produced by the beam from the other diaphragm.

The electrometer unit is identical with that previously used and accordingly needs no comment. A detailed description will be found in the paper referred to above.

The standard chamber and the roentgen tube with high voltage generator are arranged in two adjacent rooms, separated by a protective wall lined with 5 mm thick lead plate; focal distance about 540 mm. The diaphragms determining the cross section of the beams are irradiated from the tube through two small holes in this wall.

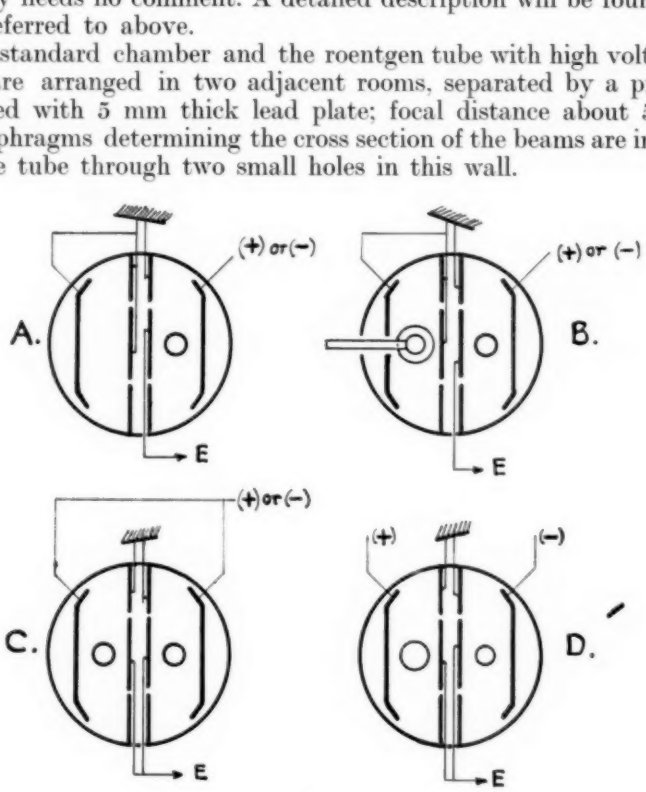

Fig. 3.

A standard chamber of the type described may be characterized as a symmetrical combination of two parallel plate electrode chambers in a cylindrical electrostatic shield. Its design permits it to be connected and used as shown in fig. 3.

1) Fig. 3 A. One of the side electrodes is connected to the plus or the minus terminal of the battery, and the other to earth. The measuring electrode opposite the charged side electrode is connected to the electrometer unit (E) and the other to earth. If one beam is allowed to pass between the charged side electrode and its opposite measuring electrode, this wiring diagram can be used in all measurements usually made with an ordinary two-electrode chamber, including calibrations of secondary

standard chambers, which for this purpose are irradiated alternately with the standard chamber.

2) Fig. 3 B. One of the sideelectrodes is connected to the plus or the minus terminal of the battery, and the other to earth. The measuring electrode opposite the charged side electrode is connected to the electrometer unit (E), and the other to earth. The beam between the central electrode and the charged sideelectrode is then used for measuring in *r*-units, and the beam between the sideelectrode connected to earth and the central electrode for irradiating a secondary standard chamber for calibrating purposes. This way of calibrating seems to be the most accurate, since both the primary and the secondary standards are irradiated simultaneously, which eliminates the influence of unavoidable intensity variations during the exposure.

3) Fig. 3 C. Both the side electrodes are connected to the plus or minus terminal of the battery, and the measuring electrodes to the electrometer unit (E). The chamber will then measure the sum of ionisation from the two beams. In cases of small intensities this wiring diagram may be of particular importance.

4) Fig. 3 D. Both the measuring electrodes are connected to the electrometer unit (E), one of the side electrodes to the plus and the other to the minus terminal of the battery. The chamber will then measure the difference of the ionisation from the two beams. In cases of equal ionisation from each beam the difference is nil. This condition is indicated by the electrometer, the string of which will then show no tendency to deviate from its zero-position.

From the above it will be seen that this type of standard chamber has a wider range of application than the ordinary two-electrode chamber. Experimental investigations briefly communicated below verify this and support the view that this type is to be preferred.

Various tests of the new measuring device

The primary interest in this new design of standard chamber undoubtedly attaches to comparisons with the old type. For this purpose six different combinations of additional filters, tube-voltages and tube currents were selected, and the corresponding intensities in *r*/min. determined by the old instrument. The old measuring electrode was then removed, the new device was inserted in the bakelite cylinder, and two consecutive series of intensity measurements were taken. Finally, the new device was removed, the old measuring electrode was again inserted, and a fourth series of measurements was taken. Each intensity value of these series is the average of three consecutive readings. The values obtained are collecteed in Table I. From its last column we get

$$\frac{\sum \frac{A_2 - A_1}{A_1}}{6} = -0.28 \text{ per cent.}$$

Table 1.

Additional filter, Tube voltage, Tube current	N:o of the series I old chamber	II new chamber	III new chamber	V old chamber	A_1 average I and IV	A_2 average II and III	$\frac{A_2 - A_1}{A_1}$ per cent
0 70 kV 4 mA	0.575	0.573	0.566	0.569	0.572	0.570	− 0.35
0 100 kV 3 mA	0.836	0.834	0.831	0.836	0.836	0.833	+ 0.36
1 Al 100 kV 5 mA	0.905	0.903	0.906	0.902	0.904	0.905	+ 0.11
4 Al 145 kV 5 mA	0.841	0.833	0.830	0.843	0.842	0.832	− 1.19
0.5 Cu + 1 Al 165 kV 5 mA	0.577	0.566	0.576	0.576	0.577	0.571	− 1.04
Tin-filter 165 kV 5 mA	0.228	0.228	0.230	0.228	0.228	0.229	+ 0.44

In comparing the series in Table I, it should be noted that the differences in intensity values do not indicate only the measuring accuracy of the two standard chambers investigated, but also the operating constancy of the high voltage generator and the accuracy with which the different combinations of tube voltage and tube current can be duplicated. The actual agreement undoubtedly justifies that the new measuring device is quite as satisfactory as the old measuring electrode, and that it may be used without introducing any additional error.

The diaphragms used for determining the cross section of the beams when measuring in *r*-units have circular apertures and are constructed as shown in Fig. 4. They are turned from pieces of type-metal, a rather hard alloy containing about 90 per cent of lead and 10 per cent of antimony.

With regard to the fact that two beams are sometimes used simultaneously, the diaphragms are made in pairs with as exactly alike apertures as possible. The diameters of the apertures were checked with

Table 2.

Diaphragm No	Diameter values		Average diameter
	1	2	
6 a	6.011	6.007	6.009
6 b	6.012	6.011	6.012
8 a	8.004	8.005	8.005
8 b	8.004	8.000	8.002
10 a	9.977	9.988	9.982
10 b	10.004	9.988	9.996
14 a	14.157	14.148	14.153
14 b	14.138	14.136	14.137

Note: The diaphragms 14 a and b are intended to have a diameter of $10 \times \sqrt{2} = 14.142$ mm.

plug-gauges, and finally determined by measurements in a comparator. Each aperture was measured along two diameters at right angles, and then the average was calculated. Table II gives the measuring results of some of the diaphragms.

Using one of the 6 mm diaphragms, intensity measurements were alternately made in the two beams I and II, both obtained with 1 Al, 100 kV and 5 mA. The results were as follows.

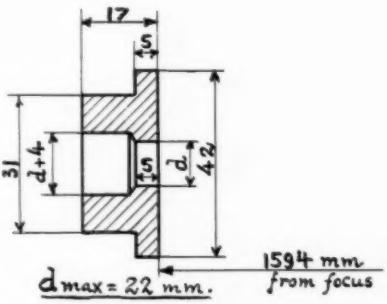

Fig. 4.

I	II	II	I	Average I	Average II
0.909	0.914	0.909	0.912	0.911	0.912

This result undoubtedly shows that the intensity of the two beams are alike within the margin of error of a standard chamber.

As noted at the bottom of Table II, diaphragms 14 a and b are intended to have an aperture with a diameter of $10 \times \sqrt{2} = 14.142$ mm. Comparing 10 b with 14 b, we find the ratio of the diameters to be $\frac{14.137}{9.996} = 1.41426$, or very nearly $= \sqrt{2}$. Inserting these two diaphragms alternately in a beam, ionisations may consequently be expected proportionate to the cross-sections of the beams, in this case $= (1.41426)^2 = 2.00013$, or very nearly $= 2$. Measurements taken gave the ionisation ratio $\frac{60.07}{30.27} = 1.986$.

The difference is less than one per cent, and that includes the operating constancy of the high-voltage generator.

The two diaphragms turned to get diameters the ratio of which is $\sqrt{2}$, are intended to be used for half-value layer (HVL) measurements with wedges of aluminium, copper or any other material desired. Since the diaphragms will give ionisation ratios very nearly = 2, all we have to do is simply to use the wiring diagram of Fig. 3 D, apply the wedge before the wider aperture, and move it to such a position that the ionisations from both the beams balance or compensate each other. Absorption in the wedge will then reduce the intensity of the wider beam by 50 %. Complete compensation is indicated by the electrometer string's not showing any tendency to deviate from its zero-position.

The wedge is moved by means of a screw, and its position is read on a millimetre scale. Before the wedge is used for HVL measurements, its absorption in some different positions must be calibrated by comparison with the absorption of plane plates of the same material. This is illustrated by the following.

An aluminium wedge was machined and ground from a 5 mm thick plate. Its ultimate dimensions were as follows: length 90 mm, breadth 40 mm, thickness 4.8 mm at the base, diminishing very nearly linearly towards its edge. A comparison of the absorption at different positions of the wedge with that of plane plates of the same material gives the diagram in Fig. 5. Using apertures not more than 15 mm in diameter, wedge positions between 25 and 90 mm may safely be used, corresponding to a continuous range of HVL-values from 0.7 to 4 mm of aluminium.

In investigating the new device, the HVL of the radiation obtained with 1 Al, 100 kV, and 5 mA, was determined by this wedge. The position giving complete compensatioin, *i. e.* 50 per cent absorption, was found to be 64.3 mm, which according to the diagram in Fig. 5 corres-

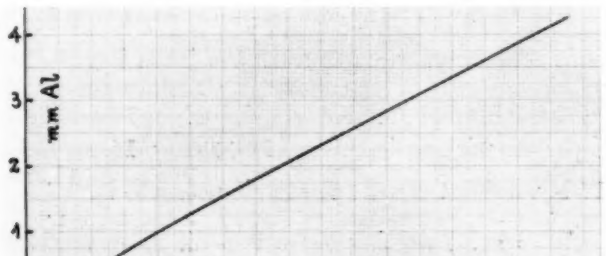

Fig. 5.

ponds to a HVL of 2.80 mm Al. From the standard absorption curves previously given by the author (*Acta Radiol.* Vol XXI, 1940, p. 603) this HVL is found to correspond to a total filtration of 1.96 mm Al. Deducting the value of the additional filter, *i. e.* 1 mm Al, gives 0.96 mm Al as the equivalent of the initial filtration of the tube. A curve obtained with the old standard chamber more than a year ago of the absorption in aluminium of a 100 kV-beam from the same tube without additional filter gave a HVL of 1.81 mm Al. According to the above mentioned standard absorption curves this value corresponds to an initial filtration equivalent to that of 0.95 mm Al, which agrees fairly well with our value.

In addition a method for general absorption measurements by the wiring diagram in Fig 3 D may be briefly mentioned. By using diaphragms of equal apertures and applying to one of the beams sectored discs or other mechanical device for the continuous modification of the intensity of the beam, the absorption in a plate applied to the other beam can easily be measured on the basis of complete compensation.

Finally, the calibration of secondary standard chambers may be briefly commented. This procedure can easily be followed by looking at Fig. 3 B. The secondary standard is inserted through apertures, provided with shutters, in the bakelite cylinder and the side electrodes into the left beam (II) at the same focal distance as the centre of the measuring electrode, where it is irradiated for a suitable time. The dose in *r*-units to which the secondary standard is exposed during this time is measured with the aid of the right beam (I), using the right half of the measuring device as a standard chamber. In practising this method, however, two conditions must be fullfilled, viz.

1) The intensities of the two beams must be the same or — if not — accurately known.

2) The right half of the device, which is used as a standard chamber, must be effectively protected from scattered radiation from the secondary standard.

As I have already said, measurements have shown that the first condition is fullfilled, in that the intensities of both the beams really are equal. Supposing, however, that this is not the case, but that the intensity of beam II (J II) is smaller than that of beam I (J I), J I and J II must be determined. This is easily done in the following way. By inserting two diaphragms of equal aperture, and using the standard chamber as shown in the wiring diagram Fig. 3 C, we get (J I + J II). Using the chamber as shown in Fig. 3 D, we get (J I — J II), and by addition of the two values we finally get J I + J II + J I — J II = 2 J I, and J I = this sum divided by 2. J II is obtained from (J I + J II) — J I, and

$\frac{J\,II}{J\,I} = þ$ is then easily calculated. We may now irradiate the secondary standard by beam II as shown in Fig. 3 B and simultaneously measure the *r*-dose by beam I. This dose multiplied by þ gives the dose to which the secondary standard has been exposed.

As regards the second condition, measurements have proved that scattered radiation from the secondary standard may increase the *r*-dose by some 5 per cent, and that this influence may be entirely eliminated by a protective layer of not less than 2 mm of lead. The above mentioned 3 mm lead plate is introduced in the central electrode to provide the protection required for this purpose.

SUMMARY

The author describes a type of standard air-ionisation chamber for roentgen ray measurements in *r*-units, which may be characterized as a symmetrical combination of two parallel plate electrode chambers in a cylindrical electrostatic shield. Certain advantages are gained by this design, particularly in measuring half-value layers and calibrating secondary standards and commercial dose-meters. The reliability of this standard chamber is illustrated by the results of various tests, and from extensive comparisons between it and the old chamber the author concludes that both chambers give identical results in *r*-units with a margin of error of about ± 1 per cent.

ZUSAMMENFASSUNG

In diesem Aufsatz wird eine Luft-Ionisationskammer für Standardmessungen von Röntgenstrahlen in *r*-Einheiten beschrieben. Die Standardkammer ist im Prinzip eine symmetrische, in einer zylindrischen, elektrostatischen Schutzhülle eingebaute Vereinigung zweier Kammern mit parallelen Plattenelektroden. Diese Konstruktion gewährt gewisse Vorteile in Bezug auf Halbwertschichtmessungen sowie Eichungen von Sekundärstandardkammern und Dosismessern. Mit Resultaten von verschiedenen Prüfungen wird die Verwendbarkeit sowie Zuverlässigkeit der neuen Standardkammer beleuchtet. Nach einem umfassenden Vergleich der neuen Kammer mit der alten Fasskammer wid festgestellt, dass beide Kammern innerhalb einer Messgenauigkeit von rund ± 1 % gleiche Resultate in *r*-Einheiten ergeben.

RÉSUMÉ

L'auteur décrit un type de chambre étalon d'aéroionisation pour la mesure des Rayons Roentgen en unités *r*. Cette chambre doit, en principe, être considérée comme la combinaison symétrique de deux chambres avec des électrodes en forme de plaques parallèles, entourées d'une enveloppe cylindrique pour la protection électrostatique. Cette construction comporte certains avantages surtout en ce qui concerne les mesures de l'épaisseur de demi-absorption, et le calibrage des chambres étalons secondaires et des dosimètres ordinaires. La valeur pratique de cette nouvelle chambre étalon et la confiance qu'on peut lui accorder sont illustrées par les résultats de diverses mesures. Il appert d'une comparaison étendue de la nouvelle chambre étalon avec l'ancienne qu'elles donnent des résultats identiques exprimées en unités *r* avec une précision de ± 1 %.

FROM THE ROENTGENDIAGNOSTIC DEPARTMENT OF THE CAROLINE HOSPITAL, STOCKHOLM
(CHIEF: PROFESSOR ÅKE ÅKERLUND)

A CONTRIBUTION TO THE ROENTGEN DIAGNOSTICS OF LIMITED ESOPHAGITIS[1]

by

Sölve Welin

The occurrence of non-specific inflammatory changes in the esophagus has long been recognized. According to BUTT and VINSON, inflammatory processes are the commonest affections of the esophagus, but it is only in the last ten or twenty years that extensive systematic investigations have been undertaken to elucidate their occurrence, pathological anatomy, and clinics. As we shall see later, neither have their roentgen pictures been very thoroughly studied.

Materials from post mortem examinations have mostly been investigated, and microscopical examination has then clearly shown that the changes found have occurred *intra vitam*. In considering them, allowance has had to be made for the possibility of the gastric juice entering the gullet after death and causing changes there; such changes are known as »oesophagomalacia acida».

The microscopic and macroscopic pictures as well as analyses of the composition and pepsin contents of the gastric juice have, however, according to a number of students — among them BARTELS, HAMPERL, MOSHER, NEUBÜRGER, SCHUBERT, BUTT and VINSON — clearly proved that the esophageal changes found really indicate an inflammatory condition, an esophagitis. Some even consider that different forms, viz. an acute, a subacute, and a chronic, can be distinguished.

The changes are mostly confined to the lower part of the esophagus. Different authors state very varying frequencies. In a series of 6,000 sections BARTELS found 82 cases of acute ulcerative esophagitis, BUTT and VINSON found 213 cases in a series of 3,032, and in a series of 100 systematically examined gullets SCHUBERT, finally, found only 37 that were absolutely free of any signs of inflammation.

[1] Submitted for publication, Jan. 15, 1946.

The great majority of these cases of esophagitis had, as far as can be ascertained, never been noticed clinically — in BUTT's and VINSON's series, for instance, only one case had been clinically diagnosed.

By collating the clinical picture and sections, it was found that the three commonest symptoms of esophagitis were *dysphagia*, which was considered to be due to an esophageal spasm caused by the inflammatory irritation, *pain*, as a rule behind the lower end of the sternum but occasionally radiating out between the shoulder blades, and *hematemesis*, which might vary considerably in volume.

The clinical study of esophagitis is obviously of much greater value, but reports of clinically observed cases are very sparse in recent literature on this subject.

In June, 1934, WINKELSTEIN read a paper to the *American Medical Association* in which he describes 5 cases of esophagitis from his own practice, of a type which did not seem to fit into the usual classification. These cases of that he designated as peptic esophagitis, had so distinctive features that they gave the impression that they probably formed a separate clinical entity. W's cases were elderly men with similar and protracted clinical histories. Roentgen examinations had shown an irregular spasm in the lower part of the esophagus, and esophagoscopy had disclosed a diffuse inflammation extending over the lower part of the mucous membrane of the gullet. Thanks to esophagoscopy, it was thus possible to distinguish these cases from the *ulcus pepticum oesophagi* group.

In the subsequent discussion, CHEVALIER JACKSON said that he had had the same experience of these esophagites as WINKELSTEIN. JACKSON further pointed out that chronic esophagitis was a common complaint due to various causes, many of which are as yet unknown or not definitely proved.

On the same occasion MOERSCH and CAMP related that they had two days earlier reported to another meeting a series of cases which had features identical with those of the group of cases reported by WINKELSTEIN. Their paper had been called »Diffuse spasm of the Lower Third of the Esophagus».

Further clinically observed cases of esophagitis are reported by SOULAS (1937) and BELINOFF (1940). The former gave a detailed account of 4 of his own cases of esophagitis — without any pathological-anatomical verification — describing among other things the roentgenological changes he had observed. The latter reported his experiences of acute catarrhal esophagitis, and pointed out that these sometimes became chronic.

As regards the roentgen diagnostics in unspecific esophagitis, PALUGYAY in his large monography »Röntgenuntersuchung und Strahlen-

behandlung der Speiseröhre», published in 1931, stated that roentgen examination of unspecific esophagitis, which according to him occurs in stenoses, diverticuli, and ectasis of the esophagus, is comparatively rare.

SCHATZKI, too, stressed in his work on the esophagus, published in 1933, that the importance of esophagitis to clinical symptomatology is underestimated, and that the number of roentgenologically demonstrated cases of this disease is fairly small. The changes in the roentgen picture are according to that author characteristic of the inflammatory process »Faltenverbreitung, Faltenstarr und Granulierung». S. also mentions that in three cases STARR had been able to demonstrate in the roentgen picture a spasm-like stenosis which he ascribed to the hyperkeratosis.

In WINKELSTEIN's cases radiography had, as mentioned above, revealed a markedly irregular narrowing of the lower third of the esophagus without any dilatation above.

In 1936 AVERY described two cases in which syphilis of the esophagus was diagnosed.

In 1938 Ross GOLDEN mentioned in »Diagnostic Roentgenology» that he had recently encountered a case with a smooth stricture in the middle third of the esophagus, which appeared quite consistent with carcinoma. Pathologic examination of the specimen, however, disclosed only evidence of chronic inflammation. He named this condition »stenosing esophagitis», and maintained that this must be a rare condition which, with Roentgen methods, cannot be differentiated from malignant disease.

The same year — 1938 — GUISEZ rendered a clinical report of »pseudocancers de l'œsophage». He pointed out that esophagitis will cause deep changes in the walls which eventually lead to stenosis, and that stenosis is most commonly due to inflammatory processes. G. further said that the Roentgen examination shows the localization and degree of stenosis — which in his experience, too, is commonest in the distal $^1/_3$ —, while esophagoscopy confirms the diagnosis. The author finally also asserted that the patients were cured by rational endoscopic treatment.

In 1940 LÜDIN described the roentgenological observation of a coarsened mucous membrane relief in a case of chronic esophagitis, with close chains of thickenings and irregular incisures due to strong pachydermia.

Since the Caroline Hospital was opened early in 1940, nine cases of diagnosed esophagitis have been examined in its Roentgen Diagnostic Department and Ear Clinic. These have all been repeatedly examined by Roentgen and subsequent esophagoscopy. In all cases the diagnosis was verified by microscopic examinations, and five were followed up for from 1 to 3 years.

No less than five of the cases had been referred from other hospitals with the diagnosis *cancer oesophagi*. All these had been examined by

Table 1

Pat.	Subjective symptoms	Length of anamnesis	Clinical diag. eventually previous Rtg diag.	Rtg finds when examined by author	Esophagoscopy	Pathologic-Anatomic Diagnosis. Test excision or p. m. examination	Controlled	Operations
E. L. J. ♂ 48 years	Progressive dysphagia	1 year	Ca. esoph. (also Rtg)	Funnel-shaped stricture. Smooth contour. Moderate dilatation	Stenosis. Easily bleeding mucous membrane	Heterotopous gastric mucous membrane. Abundant infiltrations of lymphocytes and plasma cells	1 year	
E. J. ♀ 68 years	Progressive dysphagia. Abundant phlegm belchings. Pains	4 months	Subsidiary find in Rtg of ventricle	Funnel-shaped stricture. Ragged contour. Considerable dilatation	Stenosis. Easily bleeding mucous membrane with eschar	Fibrinopurulent esophagitis	3 years	
O. L. ♂ 72 years	Progressive dysphagia. Abundant phlegm belchings. Abund. hematemesis	4 months	Ulcus ventriculi	Funnel-shaped stricture. Ragged contour. Considerable dilatation	Stenosis to the size of a knitting needle. Fibrinous mucous membrane.	P. m. examination	2¼ years	Gastrostomy after 1 year
G. V. J. ♂ 82 years	Progressive dysphagia	4 months	Ca. esoph. (also Rtg)	Funnel-shaped stricture. Ragged contour. Moderate dilatation	Stenosis. Easily bleeding mucous membrane, greyish	Heterotopous gastric mucous membrane with inflammatory changes	2 years	Gastrostomy after 2¼ years
J. Ö. ♂ 67 years	Progressive dysphagia	4 months	Ca. esoph. (also Rtg)	Funnel-shaped stricture. Slightly ragged contour. Considerable dilatation	Stenosis. Irritated, thin fibrinous mucous membrane	Strong inflamn.atory cell infiltration	8 months	
K. E. A. ♂ 66 years	Progressive dysphagia. Pains behind the sternum. Phlegm belchings	11 years	Ca. esoph. (also Rtg)	Funnel-shaped stricture	Moderate stenosis. Easily bleeding fibrin-covered mucous membrane	Fibrinoid membrane, rich in cells, with fragments infiltrated with leucocytes	2 months	
K. N. ♀ 26 years	Progressive dysphagia. Pains behind the sternum	1½ year	Dysphagia from functional causes	Funnel-shaped stricture. Slightly ragged contour. Considerable dilatation	Stenosis. Easily bleeding fibrin-covered mucous membrane	Granulation tissue with pseudomembrane	2 months	
I. P. S. ♀ 68 years	Progressive dysphagia	9 months	Ca. esoph. (also Rtg)	Funnel-shaped stricture. Ragged contour Considerable dilatation	Stenosis. Easily bleeding fibrin-covered mucous membrane	Heterotopous gastric mucous membrane	3 months	
J. V. P. ♂ 46 years	Progressive dysphagia	3 years	Esophagitis?	Slight stricture. Coarse outline of mucous membrane	Stenosis. Easily bleeding fibrin-covered mucous membrane	Loose connective tissue stroma with hypoplastic epithelium	3 years	

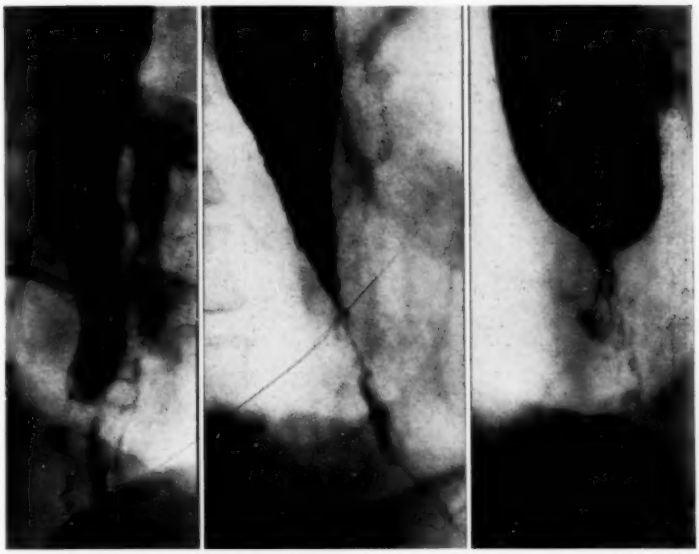

Fig. 1. Fig. 2 a. Fig. 2 b.

Fig. 1. Case 9. A radiograph of the initial stage, showing the coarse outline of the mucous membrane.

Fig. 2. a. Case 3. A radiograph of the florid stage showing the typical changes: elongated funnel-shaped constriction of the distal part, fairly distinct superior boundary, notched contour, and dilatation above.

Fig. 2 b. 2 years and 3 months later. The patient has now reached the final stage. The stricture is more pronounced, and the »funnel» greatly shortened.

roentgen, and the clinical suspicion of cancer had been declared to be confirmed roentgenologically. I have therefore considered an account of our experiences to be motivated.

As will be seen in Table 1, my material consists of three female and six male patients of very varying ages, the youngest being 26 and the oldest 82 years of age. Their average age was over 60.

The dominant symptom of these patients was progressive dysphagia. Frequently at first, it was merely a feeling of some obstruction behind the lower part of the sternum to the passage of solid food. Gradually this became worse, until only finely divided or liquid food could pass through the esophagus.

Three patients complained of pain described as a feeling of cramp behind the sternum. In the cases of short duration this was the symptom chiefly noticed by the patients, and its characteristic feature was

Fig. 3 a. Fig. 3 b. Fig. 3 c.

Fig. 3 a. Case 2. A typical radiograph of the florid stage.
Fig. 3 b. 2 months later. The constriction is now more pronounced.
Fig. 3 c. 6 months later. A picture of the final stage.

that it was equally bad whether the food was solid or liquid. The symptom varied considerably in intensity, and was occasionally so pronounced that the patients dared not eat.

Three patients complained of eructations of phlegm — these were not sour, — and one of them, who was also suffering from duodenal ulcer, was admitted to the hospital after three voluminous hematemeses.

The picture of the disease thus agrees well with that obtained in the previous, non-clinical, examinations. The more or less abundant eructations of phlegm — which in this material occurred in every third case — were really the only that had obviously not been noted earlier.

According to Dr. BERGQVIST, of the Caroline Ear Clinic, who has done the clinical investigation of this material, and to whose work I would like to refer those interested in this aspect, the esophagoscopic findings subdivide this disease into three different stages. In the initial stage the inflammatory process is less violent, and the changes are limited to an edematous, slightly bulging and easily bleeding mucous membrane.

In the second stage, which BERGQVIST designates the florid exudative

stage, the esophagoscopic picture is typical. The cranial part of the esophagus shows normal or, very rarely, slightly reddened mucosa. More distally, the mucous membrane of the more or less narrowed lumen is strongly inflamed and fibrin-covered; the border line between the normal and the inflamed mucous membrane is then as a rule very sharp, and in seven cases presented, was almost linearly horizontal.

In the final or healing stage the mucous membrane is thin, and pale scarred.

Fig. 4. Fig. 5.

Fig. 4. A 5 year old boy. Secondary esophagitis due to a congenital esophageal atresia.

Fig. 5. Secondary esophagitis, with severe dysphagia. 4 months previously total gastrectomy for cancer.

These changes in the mucous membrane are accompanied by infiltrations in the corresponding other layers of the wall. In the initial stage these are moderate, in the florid exudative stage they increase considerably, and in the final stage the wall is sclerotic and shrivelled. This increasing infiltration produces a progressive constriction of the lumen, which in the final stage may become completely obliterated.

As pointed out above, the clinical picture immediately suggests cancer. One therefore asks, whether cancer could not be differentiated roentgenologically from esophagitis. My experience of this material leads me to think that this can be done in the florid exudative and final stages. In the initial stage, on the other hand, the thick folds of the mucous membrane in the roentgen picture and the stiffness of the wall observable on the screen will hardly permit more than a probable diagnosis (Fig. 1). The changes are so pronounced, however, that they well motivate esophagoscopy accompanied by biopsy.

The roentgen pictures of the florid exudative stage have in all these cases exhibited several common features of which the most characteristic had been a fairly elongated funnel-shaped constriction in the distal part of the esopahgus (Figs. **2 a**, **3 a**, and **6 a**).

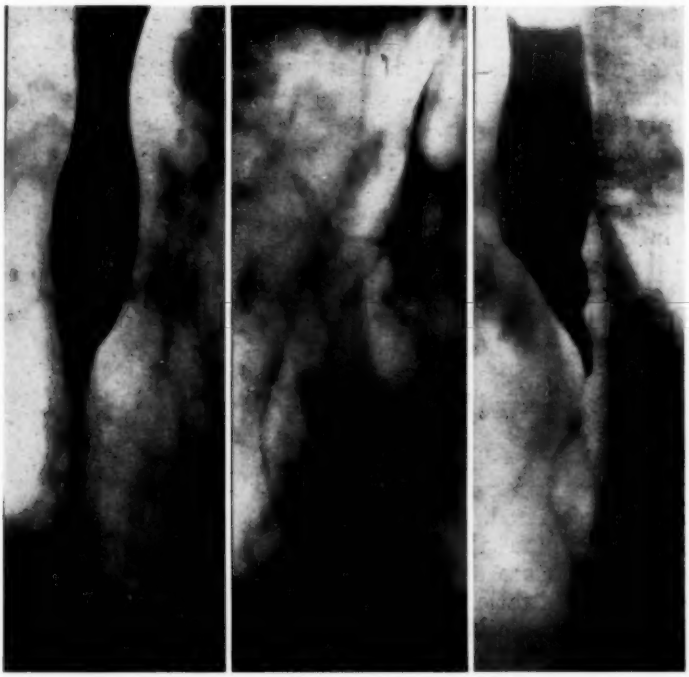

Fig. 6 a. Fig. 7 b. Fig. 6 c.

Fig. 6 a. Case 4. A radiograph of the florid stage.
Fig. 6 b. 22 months later. The stricture has disappeared after roentgen treatment. The patient free from troubles.
Fig. 6 c. 3 months later. Dysphagia has returned, with pronounced constriction.

The upper limit of that constriction has in addition been relatively distinct and as a rule at the same level all round the walls, thus giving the impression of a horizontal upper limit. In case 4 (Fig. 3 a), however, the level varied slightly from one wall of the esophagus to another, which caused some asymmetry. No upper mound-like border was demonstrated in any of the cases, and the lower limit was as a rule indefinable.

In every case there was a more or less distinct dilatation of the lumen above of the constriction. The stenosed parts of the walls were stiff and rigid. Above them, the walls were soft and pliable, giving the esophagus an outwardly convex bow-shaped contour.

Finally, all our cases presented contours of finely notched, irregular reliefs, which in the esophagoscopies undertaken in connection with the

Roentgen examinations were found to be due to membranous or pseudomembranous coatings on the inflamed and thereby greatly changed mucous membrane.

In these cases the question for roentgenologists is to find signs differentiating the condition from cancer. The presence of the above-mentioned changes characteristic of esophagitis, and the absence of the rather cuff-like with mound-like superior and inferior borders and with rather ragged contour of the mucous membrane as met with in cancer, ought in fact to make a differentiation possible.

Lye injuries and burns may also produce similar changes in the radiograph. In these cases however, the strictures due to scars are generally situated at the three physiologically narrow places and as a rule multiple. Theoretically they may of course be so localized and extensive that roentgenological differentiation from esophagitis is impossible, but in such cases the clinical history will distinguish between the two affections.

The secondary esophagities too, may give the same roentgen picture as the primary. Fig. 4 illustrates this. This was a boy of 5, whose secondary espophagitis was the result of congenital esophageal atresia.

Another of our cases of secondary esophagitis was a woman, on whom a total gastrectomy for cancer had been performed four months earlier. The patient was now complained of severe dysphagia. Clinically, a recidivation in the stump of the esophagus was suspected, but the roentgen diagnosis established that instead it was a case of esophagitis (Fig. 5).

As already said five of my nine patients were followed up roentgenologically for from one to three years; in three of them it was possible to see that the constriction of the affected part of the esophagus had progressed, although esophagoscopy had shown that the inflammatory changes in the mucous membrane had been improving during the treatment.

Case No. 3 had thus when examined by roentgen in June, 1942, presented the picture shown in Fig. 2 a. The changes indicated by the roentgen picture are typical of esophagitis in the florid exudative stage. A roentgen examination in August, 1944, showed that the process had progressed considerably, and on that occasion the changes were those characterising the »final» stage, viz. a lumen constricted to the size of a knitting needle, a very great shortening of the »funnel» proper and increased dilatation cranially of the constriction. The scar in the healing mucous membrane was at the same time visible in the esophagoscope. As early as a year before this last roentgen examination the patient's severe dysphagia had necessitated gastrostomy. In May, 1945 — ten months after the last roentgen examination —, the patient died of hemorrhage due to arrosion of an artery in a duodenal ulcer. The post mortem examination (No. 96/1945) revealed complete obliteration of the

esophageal lumen for barely ten cm just above the heart, where the wall of the esophagus was greatly thickened and sclerotic. Neither macroscopically, nor microscopically could any signs of cancer be detected.

Figs. 3 a, b, and c show that in Case 2 the disease had also progressed in spite of all therapy.

In Case No. 4 the diagnosis *cancer oesophagi* was made from a roentgen examination in August, 1943 (Fig. 6 a). In the esophagoscopical examination three days later no definite tumourous excrescences could be seen in the area observed, but the endoscopist gained the impression that a solid infiltrating process was about to break through in the most constricted part. For this reason, and in view of the roentgen diagnosis of cancer, the patient was given very strong roentgen treatment (4.764 r on 7 fields in 31 days), although the biopsy made in the esophagoscopy showed no signs of malignancy, but on the contrary indicated fairly abundant inflammatory changes. In control examinations in June, 1944, and June, 1945 (Fig. 6 b), the constriction had disappeared, and the contrast passed down without any obstruction. On the screen, however, a very stiff wall could on both occasions be observed in the previously constricted part. On re-examining the roentgen pictures taken in August, 1943, the primary picture was found to be like those of our other cases of esophagitis. There is accordingly no reason to think that this had been anything but a case of esophagitis. The question then arises whether the roentgen treatment might conceivably in this case have prevented stenosis by the therapeutical effect of the roentgen rays. Three months later — $^{30}/_{12}$, 1945, — the patient returned with severe dysphagia, however, and that time the roentgen examination (Fig. 6 c) disclosed a pronounced stricture, and gastrostomy was found necessary.

Judging by our experience from this material, the prognosis in this disease is thus as the obstructive effects are concerned is very serious notwithstanding the histological benign nature of the process — a fact which has not been known before, and which in a large number of cases will sooner or later necessitate gastrostomy.

SUMMARY

The clinical picture of esophagitis is such that clinicians will initially suspect of a malignant process. According to the author, who bases his opinion on nine pathologically-anatomically verified cases, the roentgenological changes are characteristic in the more advanced cases of this disease. They are: an elongated funnel-shaped constriction with notched contours in the distal part of the esophagus, a relatively distinct superior boundary and a dilatation cranially of the process. A diagnosis differentiating esophagitis from cancer is therefore possible, and some cases that used to be diagnosed as cancer can accordingly henceforth be excluded from that diagnosis.

Notwithstanding the benign histological nature of the process the prognosis is very serious, and in a large number of cases gastrostomy will sooner or later be necessary.

ZUSAMMENFASSUNG

Das klinische Bild einer Ösophagitis ist derartig, dass der Kliniker in erster Reihe an eine bösartige Geschwulst denkt. Laut Verf., der sich auf ein Material von neun pathologisch-anatomisch kontrollierten Fällen stützt, sind die röntgenologischen Veränderungen bei den weiter vorgeschrittenen Fällen dieser Krankheit charakteristisch. Sie bestehen in einer länglichen, dütenförmigen Verengerung mit zackiger Kontur in der distalen Partie der Speiseröhre mit verhältnismässig scharfer oberer Begrenzung, sowie in einer Erweiterung kranial von dem Prozess. Eine Differentialdiagnose zwischen Ösophagitis und Krebs ist hiernach möglich, und es lassen sich also von jetzt an gewisse Fälle, die früher zum Krebs gerechnet wurden, von Diagnose streichen.

Die Prognose dieses Leidens ist trotz der histologischen Gutartigkeit des Prozesses überaus ernst, und in vielen Fällen wird früher oder später eine Gastrostomie notwendig werden.

RÉSUMÉ

Dans les œsophagites le tableau de la maladie est tel que les cliniciens pensent avant tout à une néoformation maligne. Selon l'auteur, qui s'appuie sur un matériel de neuf cas vérifiés anatomo-pathologiquement, les images rœntgenologiques de l'affection sont caractéristiques dans les cas assez avancés. Elles consistent en un rétrécissement allongé en forme d'entonnoir, à contours vermoulus, dans la partie distale de l'oesophage, avec une limite supérieure relativement distincte et une dilatation en amont de la lésion. Dès lors un diagnostic différentiel entre oesophagite et cancer est possible, et l'on pourra désormais s'abstenir de ranger parmi les tumeurs malignes un certain nombre de cas que jusqu'ici on avait placés dans leur catégorie.

Malgré la bénignité histologique du processus le pronostic de l'affection est remarquablement sévère, et dans une forte proportion des cas la gastrostomie s'impose tôt ou tard.

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Supplements to the

ACTA RADIOLOGICA

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